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## Original Communications

### TRIALS WITH PENICILLIN IN THE TREATMENT OF PRE-ECLAMPSIA AND ECLAMPSIA

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ON THE basis of various lines of evidence accumulated in the study of human menstrual cycles and pregnancy,[1, 2, 3] we have advanced the hypothesis that the precipitating cause of late pregnancy toxemia is the release from the uterus into the general circulation of a toxic product of tissue catabolism identical to the highly toxic atypical euglobulin demonstrated by us in menstrual discharge.[4] The recent discovery of a striking antitoxic action of penicillin in rats given lethal doses of menstrual toxin led to the therapeutic trials to be reported. The details of this discovery and the demonstration that this antitoxic action is not a bactericidal effect were reported at the September, 1951, meeting of the Laurentian Hormone Conference.[5] Thus far a total of eight patients with late pregnancy toxemia have been studied and their response to penicillin therapy investigated. Two of these had eclampsia, four had severe pre-eclampsia and two had early mild signs when treatment was started.

#### Method of Study

Before penicillin was administered, a control period of observation after admission to the hospital was carried out in each case. This included a urine culture to be sure that urinary tract infection was not involved, a series of

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quantitative determinations of urinary albumin,* blood pressure recordings, daily weight, and an accurate record of fluid balance. The effect of routine care of toxemia and of any other measures that the obstetrician wished to try on the course of the disease was first determined and only those patients who failed to show improvement were given penicillin.

## Presentation and Discussion of Cases

CASE 1 (Fig. 1).—Mrs. M. Z., aged 24 years was first seen in the outpatient clinic in April, 1951, during the sixteenth week of her third pregnancy. She had miscarried at the eighth week in 1948, and her second pregnancy, in 1949, had terminated spontaneously during the thirty-fourth week with fulminating toxemia and stillbirth. The course of this pregnancy was normal until the thirtieth week when her blood pressure rose to 135/95, accompanied by excessive recent weight gain but no albuminuria. One week later her blood pressure was 140/110 and 4+ albuminuria had developed together with edema, lower abdominal pain, and backache. She was admitted and within 14 hours rapidly progressed to a "Grade II" pre-eclampsia with increasing subjective symptoms including frontal headache and blood pressure readings up to 180/120. She was given magnesium sulfate with some lowering of pressure (160/100-110) but no other improvement.

No magnesium sulfate was given after the beginning of our control studies, at 2 P.M. of her second day in the hospital. During the following 26 hours before penicillin was started the only clinical improvement was a drop in systolic pressure to 140 to 145 mm. Hg. The diastolic pressure and symptomatology remained unchanged. Her rate of albuminuria showed the diurnal rhythm typical of toxemic patients, i.e., highest during the evening and lowest in the early morning hours. The specimen collected at 2 to 4 P.M. on August 8 contained considerably more protein than the corresponding specimen of the previous day, indicating that her rate of excretion was progressing rapidly. Therapy with penicillin, started at 4 P.M., was followed by an immediate drop in urinary albumin, a marked diuresis and a very noticeable improvement in her appearance and symptomatology. During the following 10 days, while therapy was continued, her albuminuria remained low except for one rise at 12 to 8 A.M. on August 10 when there was an 8-hour interval between injections of penicillin. Diastolic blood pressure, which went below 100 only after penicillin was given, showed sporadic rises during the first 3 days of therapy but stabilized thereafter. A decrease in fetal movements was noted by the patient on August 17 and 18 followed by loss of the fetal heart sounds at midnight on August 18, after which penicillin was discontinued. On August 21 she was discharged from the hospital and was readmitted in labor one week later when she delivered a 2 pound, 3 ounce, macerated fetus. Six weeks post partum there was no albumin in the urine and the blood pressure was normal.

Despite the fact that a very satisfactory control of severe toxemia appeared to be instituted and maintained by penicillin therapy in this case, the

*Orders were given for the collection of all urine and the rate of protein excretion was followed at 4-hour intervals. The albumin to creatinine ratio was used as an index of proteinuria because complete and accurate collections on a busy obstetrical service are practically impossible. Since urinary creatinine in most women approximates 1.0 gram per 24 hours (regardless of urine volume, diet, or activity), this ratio roughly corresponds to the rate of protein excretion in grams per 24 hours. The total protein in each 24-hour collection was also determined, and the collected 24-hour volume corrected when necessary on the basis of its creatinine content. Urinary albumin was measured by reading the degree of turbidity on a Coleman junior spectrophotometer after the addition of 5 per cent sulfosalicylic acid, a calibration curve with standard protein solutions having been previously established and the unknown values determined from it. Creatinine determinations were also performed on the spectrophotometer against a standard creatinine calibration curve, using a modification of the original Folin method for visual colorimetry.

We cannot overemphasize the value of creatinine determinations in any quantitative study of urinary constituents. Results expressed in terms of milligrams per cent can be very misleading since they are entirely dependent upon the fluid output which is subject to marked variations. Accurate collections of all urine excreted over a given period and the expression of results in terms of milligrams per hour would overcome this difficulty. Even under the most carefully controlled conditions, however, a gross error in collections may be made that will confuse the findings. The only satisfactory solution of this problem, in our experience, lies in performing a creatinine determination upon every specimen and correcting the volume accordingly. Variations in creatinine output, although they do exist, are not of sufficient magnitude to influence appreciably the values for albuminuria and are certainly of minor importance when compared with the gross errors introduced by inaccurate collections.

fetus died in utero. The failure to survive, however, is not surprising in the light of the pathological findings in the placenta. In the decidual portion were noted thrombosis, necrosis, and hemorrhage quite similar to that found in the menstruating endometrium. The trophoblast showed "fibrinoid degeneration of the ceiling, septum, and floor." Although obviously premature (12 by 10 by 2 cm.) the placenta contained areas of relative maturity and syncytial degeneration (Tenney changes). It is safe to assume that these changes preceded the appearance of toxic signs in this patient and had advanced to an irreversible stage by the time our studies began. Penicillin in large doses appeared to have neutralized the effect of circulating toxin sufficiently to control the maternal signs and symptoms, but could not reverse the pathological intrauterine processes which proceeded to deprive the fetus of the necessary support. We have long felt that death of the fetus, with its usual accompaniment of a decrease in signs of toxemia, may reflect sealing off of blood supply at the placental site to the point that sufficient maternal blood fails to reach the villi and the decidual toxin ceases pouring into the maternal circulation. Such a situation would explain the fact that there was no recrudescence of toxemia in this patient after death of the fetus when penicillin was discontinued.

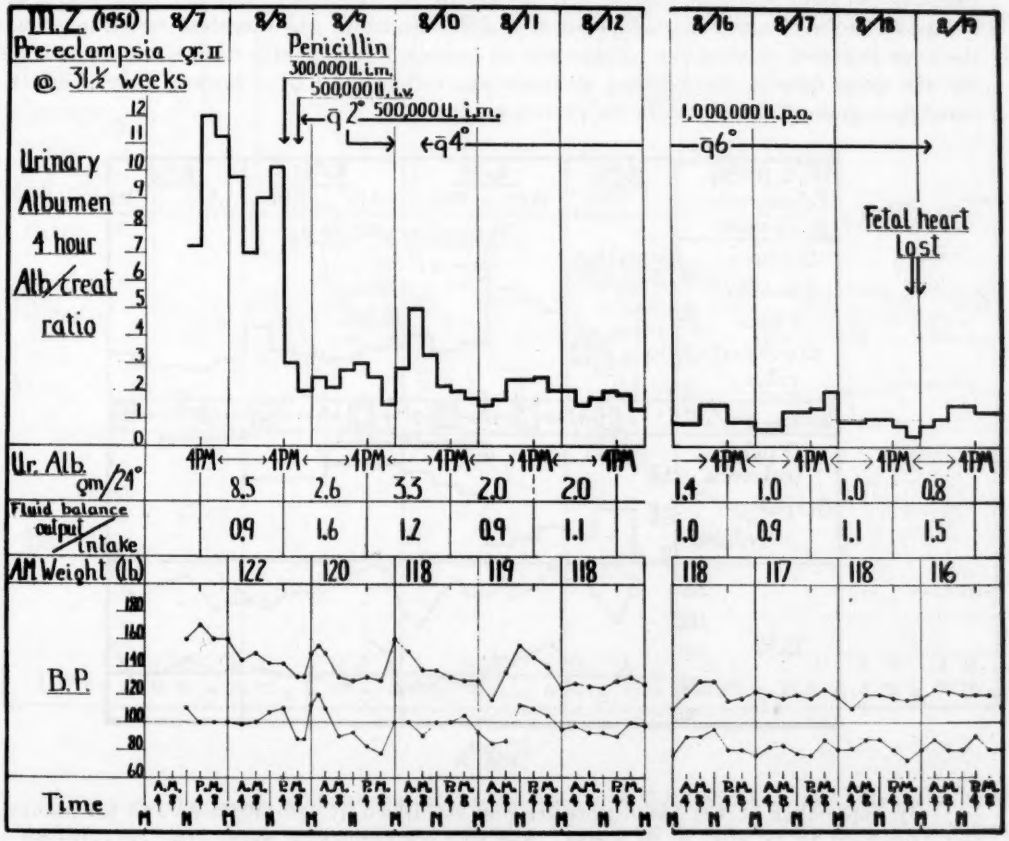



Fig. 1.

CASE 2 (Fig. 2).—Mrs. M. S., aged 24 years, gravida i, was a patient at the New England Hospital, to the staff of which we are indebted for cooperation in her study and treatment. She was first seen in the clinic on Aug. 22, 1951, when she was 34 weeks pregnant by dates, with a normal blood pressure and no albuminuria. She weighed 180 pounds, however, and was given dietary instructions including the omission of salt.

On August 28 she called the hospital because of sudden severe headache. At 2 P.M. she had a convulsion and was admitted 15 minutes later in a semicomatose condition with a blood pressure of 160/96, pitting edema of the lower extremities, and twitching of the hands and face. An accurate study of her albuminuria and fluid balance was instituted from the moment of admission. She was immediately given sedatives and magnesium sulfate intravenously, followed by a constant intravenous infusion of 10 per cent glucose. Despite these measures the first 22 hours in the hospital were accompanied by no clinical improvement beyond the absence of further convulsions. Urinary albumin showed the typical evening rise and early morning drop but was higher in the 8 A.M. to 12 noon specimen on August 29 than it had been at 2 to 4 P.M. of the previous day. Her intake-output chart showed progressive retention of fluids and her diastolic pressure had risen to around 110 mm. Hg. Because of her critical condition she was not weighed. Penicillin was started at noon on August 29 with 1 million units intravenously and 1 million units intramuscularly, followed by 1 million units intramuscularly at 2-hour intervals thereafter. Diuresis, decreased albuminuria, and a drop in diastolic pressure were apparent in the first 4 hours of treatment. By 7 P.M. she became responsive and was able to take fluids by mouth. The systolic pressure had dropped and the diastolic stabilized at 90 to 100 mm. Hg. Lowered albuminuria, diuresis, and general improvement continued but a rise of pressure between midnight and 4 A.M. on August 30 was noted; and the fetal heart, with a rate of 140 at 1 A.M., was not heard at 8 A.M. Penicillin was therefore discontinued with the noon injection on that day. There was an increased albuminuria from 8 P.M. to midnight, but the usual drop in the morning specimen was accompanied by a marked diuresis and followed by a gradual diminution in the protein output.

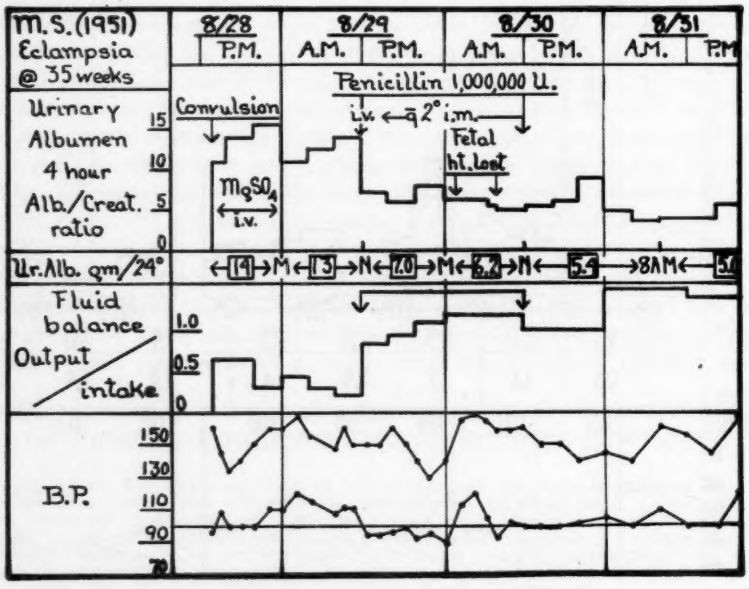



Fig. 2.

By September 15 the blood pressure had stabilized at 120-140/80-90 and albuminuria had decreased to 2.0 Gm. in 24 hours. She was discharged on September 18, returned to the clinic for weekly check-ups and was admitted in labor on October 6, 3 days after the expected date of confinement, when she delivered a 5 pound, 1 ounce, macerated fetus. Six weeks post partum she was free of hypertension and the urine contained no protein.

Here again, as in the case of Mrs. M. Z. (Fig. 1), diuresis, decreased albuminuria, clinical improvement, and a drop in diastolic pressure appeared

to be associated with penicillin therapy, but with no benefit to the fetus. The subsequent temporary rise in pressure, associated as it was with loss of the fetal heart sounds, suggests that a process involving increased toxin production within the uterus may have sealed off more blood supply to the intervillous spaces, thus accounting for intrauterine asphyxiation of the fetus, and for the fact that toxic signs did not recur in as severe a form as prior to penicillin therapy.

CASE 3 (Fig. 3).—Mrs. L. F., aged 30 years, was sent to the Boston Lying-in Hospital by her local doctor on August 29, when she was 33 weeks pregnant, with a blood pressure of 240/120, a 4+ albuminuria and transient headaches with scotomas. She weighed 204 pounds, having gained 23 during this pregnancy despite dietary restrictions including the omission of salt. She had had hypertension since the age of 16 years. Her blood pressure was elevated (150/100) early in pregnancy, but the very high readings on admission and the albuminuria and headaches were of recent development. Her only previous pregnancy had terminated at 12 weeks with a spontaneous miscarriage.

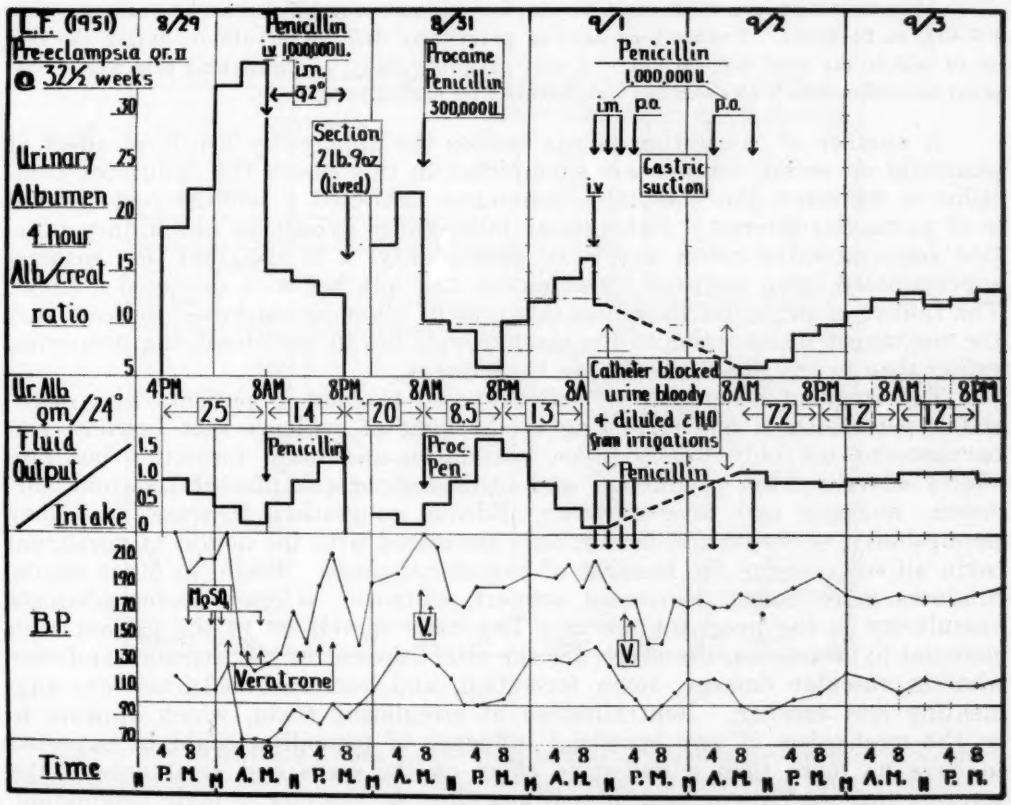



Fig. 3.

An accurate study of her rate of albuminuria and fluid balance was started at the time of entry together with intensive therapy with magnesium sulfate and Veratrone. In the 16 hours before penicillin was given a spectacular drop in blood pressure from the Veratrone occurred. During this time, however, her rate of proteinuria and fluid retention was progressing to an alarming degree. At 8 A.M. on August 30 1 million units of penicillin were given intravenously and another million by intramuscular injection, followed by 1 million units intramuscularly every 2 hours for the 12 hours prior to cesarean section. A decreased output of urinary protein and an increased excretion of urine were apparent

from the start of injections. Neither penicillin nor continued Veratrone, however, prevented a recurrent rise in systolic pressure, although the diastolic remained below 100 mm. Hg. A cesarean section was performed at 8 P.M. and a 2 pound, 9 ounce, infant delivered who survived. During the 12 hours following section albuminuria, hypertension, and fluid retention again became progressive and were again reversed after penicillin and Veratrone therapy. The penicillin may be assumed to have been responsible for the diuresis and decreased albuminuria since Veratrone had already been shown to have no influence on these two signs. During the night (August 31 to September 1) the patient's clinical condition again became worse with increasing albuminuria, fluid retention, and a rise in diastolic pressure. This time, penicillin was started 4 hours before any Veratrone was given, and was followed by a drop in blood pressure as well as a diuresis and decreased albuminuria. Penicillin therapy was discontinued on September 2. A subsequent increase in protein excretion to a level of 12 Gm. per 24 hours and sporadic rises in diastolic pressure to readings as high as 130 mm. Hg persisted for five days. On the fifth day a profuse vaginal flow was followed by a pronounced decrease in albuminuria and stabilization of blood pressure.

At examination six weeks post partum her pressure was 158/100 and urinary albumin 2.0 Gm. in 24 hours. Twenty-four days of practically daily observations, during the last 10 of which she took 800,000 units of oral penicillin daily, revealed that this was a constant condition which was entirely uninfluenced by penicillin therapy.

A number of interesting points besides the apparently beneficial effect of penicillin on severe toxemia are exemplified in this case. The failure of penicillin to influence the residual albuminuria exhibited 2 months post partum is of particular interest. Although an intravenous pyelogram and kidney function tests failed to reveal any renal abnormality, it is apparent that toxemia superimposed upon essential hypertension had left her with damaged kidneys. The failure of penicillin to reduce this type of albuminuria would indicate that the mechanism of its action in the toxemic state lies in its detoxifying properties rather than in any direct effect upon the kidneys.

The frequent occurrence of superimposed toxemia in patients with essential hypertension is not surprising in the light of evidence that vascular embarrassment not only favors tissue breakdown and toxin formation but also affects adversely the production and utilization of the placental steroid hormones, estrogen and progesterone.[3] Edema, congestion, increased capillary permeability, necrosis, and hemorrhage associated with the action of menstrual toxin all come under the heading of vascular damage. Toxin, in other words, produces more toxin. Hormonal support, moreover, is essential for adequate vascularity in the pregnant uterus. The stage is well set in the patient with essential hypertension, therefore, for the establishment of the toxemic syndrome wherein vascular damage, toxin formation, and hormonal deficiency are augmenting one another. Neutralization of circulating toxin, which appears to be the mechanism of any beneficial influence of penicillin, could be expected to have no more than a palliative effect on the signs and symptoms of the severely toxemic patient, and little if any effect on the rate of toxin production.

A third point of interest in this case was the immediate postpartum recrudescence of toxemia. This appeared to be interrupted by penicillin therapy, but terminated only by the bout of profuse vaginal bleeding that occurred one week after delivery. Emptying of the uterus constitutes removal of the placental source of steroid hormones without necessarily the complete removal of the decidua. Pathological examination of the placenta revealed thrombosis, necrosis, and hemorrhage in the decidual portion quite analogous to that found in the menstruating endometrium. Removal of hormonal support without complete removal of the source of the toxin might be expected to be accompanied by a persistence or exacerbation of the toxemic syndrome.

CASE 4 (Fig. 4).—Mrs. R. E., aged 23 years, gravida i, was first seen at the Boston Lying-in Hospital when she was 21 weeks pregnant. Her prenatal course was normal until the thirty-sixth week when she was admitted because of albuminuria and a rise in blood pressure.

Accurate study of her albuminuria and fluid balance, with the idea of instituting penicillin therapy, revealed fluid retention and the diurnal rhythm of protein excretion typical of toxemia. Since bed rest and routine toxemic care, however, were accompanied by a drop in blood pressure, an increased output of urine, and a decreased albuminuria, no penicillin was given at this time. During her stay in the hospital she was taught to keep an accurate record of her fluid intake and to collect 24-hour urine specimens. She was discharged much improved on the sixth day with instructions to return to the clinic twice weekly bringing with her a 24-hour specimen of urine and a record of fluid intake. Albumin and sodium "pregnanediol" glucuronide (NaPG) were measured in five specimens during the following 18 days. Her "pregnanediol" was dropping, but this was considered normal since she was so close to term. There was no rise in blood pressure or excessive weight gain. Her albuminuria, however, increased steadily, and she was showing a progressive retention of fluid.

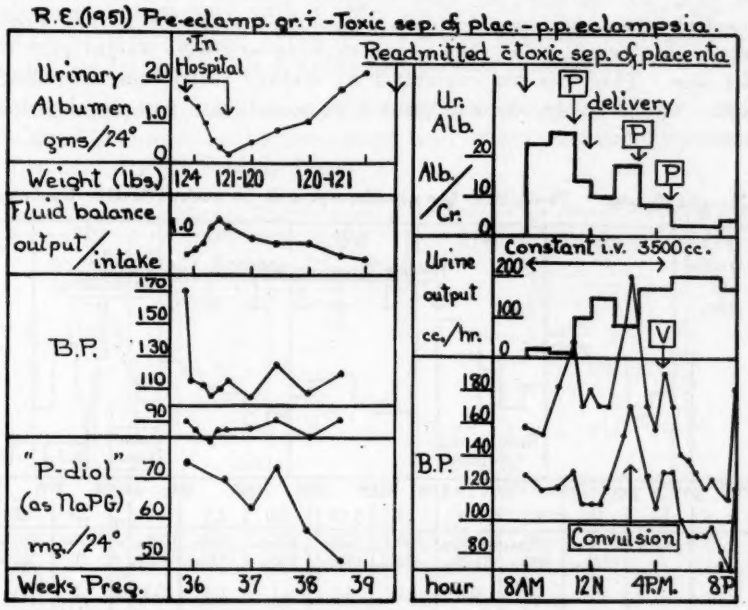


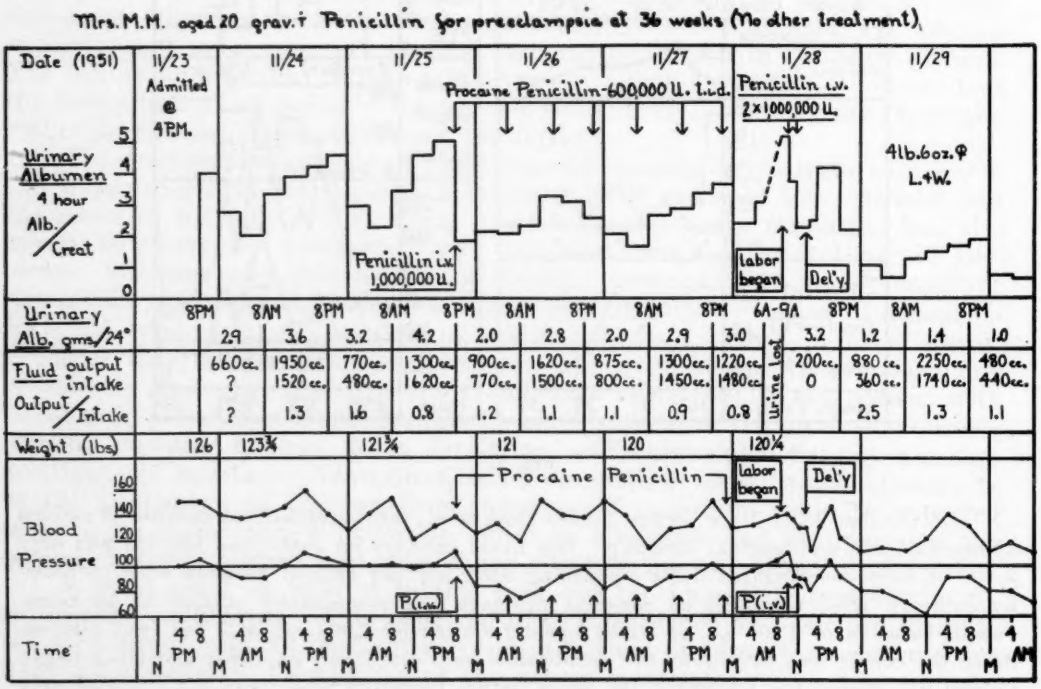

Fig. 4.

On October 15 at 7 A.M., when 3 days from term, she was admitted because of sudden abdominal pain and vaginal bleeding. Her blood pressure on entry was 158/128 and only 5 c.c. of very concentrated urine containing 2,000 mg. per cent of albumin were obtained by catheter. She was kept on constant drainage and immediately started on an intravenous infusion of 1,500 c.c. of whole blood followed by 2,000 c.c. of 5 per cent glucose. Since the cervix was favorable, the membranes were artificially ruptured and labor began promptly. During the following 2½ hours before penicillin was given she excreted only 15 c.c. of urine, 10 c.c. during the first hour and 5 c.c. during the period from 9 to 10:30 A.M. Her rate of albuminuria was increasing, the blood pressure was rising, and she was bleeding bright red blood from the vagina. One million units of penicillin at 10:30 A.M. were followed by a marked decrease in proteinuria, a drop of both systolic and diastolic pressures, and the excretion of 100 c.c. of urine during the last hour of active labor before delivery of a 5 pound, 2½ ounce, healthy infant. There was no excessive blood loss during

or after delivery and the decreased albuminuria and increased urine output continued for 2 hours post partum. In the specimen collected from 1:30 to 3 P.M., however, 3 to 4½ hours after the penicillin had been injected, fluid retention and increased proteinuria became apparent. This was accompanied by an alarming rise in blood pressure to 250/170 and a convulsion at 2:30 P.M. At 3 o'clock she was given 500,000 units of penicillin intramuscularly followed by a second drop in albuminuria and increase in urine output. Blood pressure remained unstable but was lowered following the administration of Veratrone plus another 500,000 units of penicillin at 5 P.M. and twice more during the next 12 hours. Thereafter she had an uneventful postpartum course and was discharged 13 days after delivery with a normal blood pressure and no albuminuria.

Diuresis, a drop in blood pressure, and a decreased proteinuria followed the prepartum administration of 1,000,000 units of penicillin to this patient despite the fact that active labor, which ordinarily aggravates anuria, hypertension, and albuminuria, was in progress. We would like to think that had we continued intensive penicillin therapy, giving no less than 1,000,000 units every 2 hours, the postpartum flare-up and convulsion might have been averted.

CASE 5. (Fig. 5).—Mrs. M. M., aged 20 years, gravida i, was first seen at the Boston Lying-in Hospital when she was 16 weeks pregnant, and had a normal prenatal course until her twenty-third week. She then began showing excessive weight gain with marked edema of the legs. This was not controlled by dietary restrictions including the interdiction of salt. By 35 weeks she had gained 28 pounds and had developed albuminuria and hypertension.


Mrs. M.M. aged 20 grav. i Penicillin for preeclampsia at 36 weeks (No other treatment)
Date (1951)
11/23 Admitted @ 4 P.M.
11/24
11/25
11/26
11/27
11/28
11/29
Procaine Penicillin-600,000 U. t.i.d.
Penicillin i.v. 2×1,000,000 U.
4lb.6oz.↑ L.+W.
Urinary Albumen 4 hour Alb./Creat
Penicillin i.v. 1,000,000 U.
labor began
Del'y
Urinary Alb. gms./24°
2.9 3.6 3.2 4.2 2.0 2.8 2.0 2.9 3.0 3.2 1.2 1.4 1.0
Fluid output / intake
660cc. 1950cc. 770cc. 1300cc. 900cc. 1620cc. 875cc. 1300cc. 1220cc. 200cc. 880cc. 2250cc. 480cc.
? 1520cc. 480cc. 1620cc. 770cc. 1500cc. 800cc. 1450cc. 1480cc. 0 360cc. 1740cc. 440cc.
Output / Intake
? 1.3 1.6 0.8 1.2 1.1 1.1 0.9 0.8 2.5 1.3 1.1
Urine lost
Weight (lbs)
126 123¾ 121¾ 121 120 120¼
Blood Pressure
Procaine
Penicillin
labor began
Del'y
P(i.v.)
P(i.v.)
Time
N PM 4 8 M AM 4 8 N PM 4 8 M AM 4 8 N PM 4 8 M AM 4 8 

protein excretion with the typical diurnal rhythm. From 8 A.M. to 8 P.M. of the second day she was again retaining fluid and began complaining of transient headache and epigastric pain. At 8 P.M. 1 million units of penicillin were given intravenously together with 600,000 units of procaine penicillin by intramuscular injection. There was an immediate drop in albuminuria, rather than the usual increase from 8 P.M. to midnight, a 30 mm. drop in diastolic pressure, and an increased output of urine in relation to fluid intake. Injections of procaine penicillin, 600,000 units every 8 hours for the next 2 days, appeared to keep signs of toxemia under control and there was no further complaint of headache or epigastric pain. No penicillin was given the morning of November 28 since interruption of pregnancy had been decided upon. The membranes were artificially ruptured at 8 A.M. One specimen of urine was lost prior to the insertion of an inlying catheter. Uterine contractions began soon after and were accompanied by a marked increase in proteinuria and a rise in diastolic pressure to 110 mm. Hg. At 10 A.M. and again at 12 noon 1 million units of penicillin were injected intravenously. The pronounced decrease in albuminuria and drop in diastolic pressure prior to a precipitous delivery at 1 P.M. and in spite of active labor could be accounted only to the penicillin. Urine collected 4 to 8 hours after the last injection again contained a large amount of albumin and the blood pressure also rose at this time. By the third day post partum, however, albuminuria had disappeared and she was discharged 7 days later with a blood pressure of 120/90. The infant, a 4 pound, 6 ounce, female at birth, gained 1 pound in 4 weeks and was then taken home by the mother who did not return for her 6 weeks post partum examination.

The observations in this case call for no comment. There would seem to be little room for doubt as to the cause and effect relationship between penicillin therapy and the clinical findings.

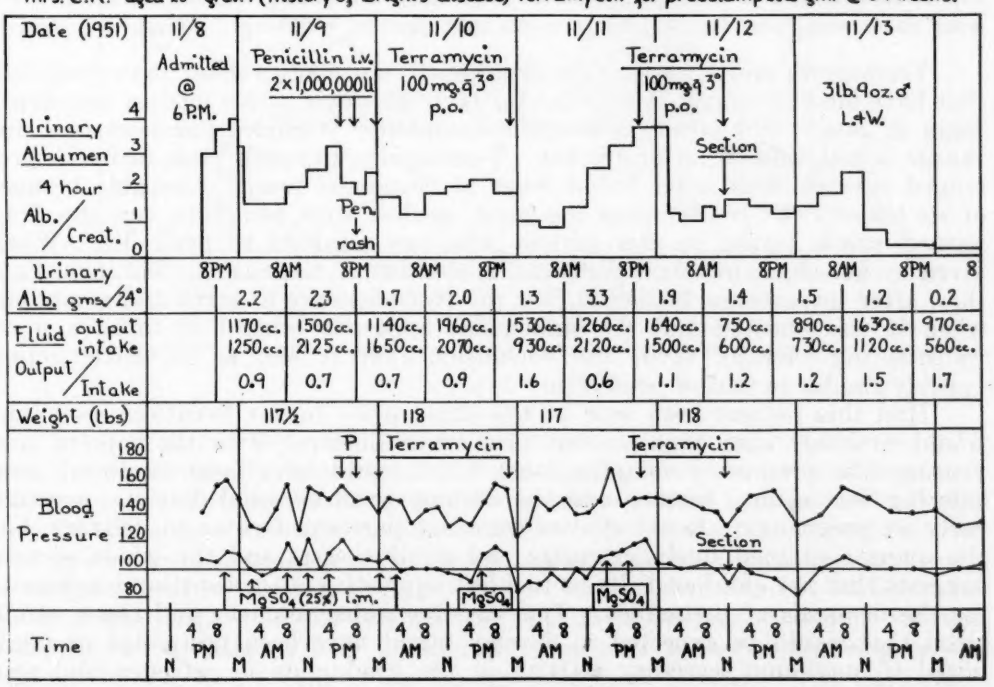

Mrs. E.R. aged 20 grav.i (History of "Bright's" disease) Terramycin for preeclampsia gr.ii @ 34 weeks.
Date (1951)
11/8
Admitted @ 6 P.M.
11/9
Penicillin i.v. 2×1,000,000 U
11/10
Terramycin 100 mg. q 3° p.o.
11/11
Terramycin 100 mg. q 3° p.o.
11/12
Section
11/13
3 lb. 9 oz. ♂ L.&W.
Urinary Albumen
4 hour Alb./Creat.
Pen. rash
Urinary Alb. gms/24°
2.2 2.3 1.7 2.0 1.3 3.3 1.9 1.4 1.5 1.2 0.2
Fluid output / intake
1170 cc. / 1250 cc.
1500 cc. / 2125 cc.
1140 cc. / 1650 cc.
1960 cc. / 2070 cc.
1530 cc. / 930 cc.
1260 cc. / 2120 cc.
1640 cc. / 1500 cc.
750 cc. / 600 cc.
890 cc. / 730 cc.
1630 cc. / 1120 cc.
970 cc. / 560 cc.
Output / Intake
0.9 0.7 0.7 0.9 1.6 0.6 1.1 1.2 1.2 1.5 1.7
Weight (lbs)
117½ 118 117 118
Blood Pressure
P
Terramycin
Terramycin
Section
MgSO4 (25%) i.m.
MgSO4
MgSO4
Time
N PM M AM N PM M AM N PM M AM N PM M AM N PM M AM N PM M AM

Fig. 6.

CASE 6 (Fig. 6).—Mrs. E. R., aged 20 years, gravida i, was first seen at the Boston Lying-in Hospital Aug. 8, 1951, in her twenty-second week of pregnancy. Her blood pressure was above normal at that time (124/90) and she gave a history of "Bright's

disease'' in childhood. The blood pressure was higher at each succeeding visit and she was put on a salt-free diet in an attempt to control excessive weight gain and edema. Headache, nausea, and albuminuria developed at 34 weeks and she was admitted to the hospital.

During the first 24 hours, despite magnesium sulfate therapy, the subjective symptoms became more severe and the blood pressure unstable, with diastolic readings varying from 100 to 120 mm. Hg. The rate of protein excretion, which showed the usual diurnal rhythm, was as high at 4 to 6 P.M. of the second day as it had been at 6 to 8 P.M. on the day of entry. The expected further rise from 6 P.M. to midnight appeared to be prevented by two intravenous injections of penicillin at 6 and at 8 P.M. By 9 P.M. the headache was better and she was able to retain food. A skin rash had developed, however, presumably from the penicillin, which was discontinued. Oral terramycin, 100 mg. every 3 hours, was substituted, since we had experimental evidence that it had the same detoxifying property as penicillin. During the following 24 hours of terramycin medication and for 8 hours thereafter, hypertension (with the exception of one period in the later afternoon), albuminuria, and fluid retention were controlled considerably better than they had been by magnesium sulfate. The severe frontal headache disappeared and she had no nausea. In the afternoon of November 11, when she had had no terramycin since the night before, there was a recrudescence of signs and symptoms. They failed to be influenced by magnesium sulfate but appeared to be controlled again by terramycin which was given over a 15-hour period prior to delivery by cesarean section at noon on November 12. There was an increased excretion of protein the morning after delivery but the urine contained no albumin 2 days later, although the diastolic blood pressure was still high (90 mm. Hg) when she was dismissed from the hospital 13 days post partum.

Four weeks later, when seen in the clinic, blood pressure was 140/100 and the patient had 1+ albuminuria in a voided specimen. The baby, a 3 pound, 9 ounce, female at birth went home well from the hospital 8 weeks post partum, weighing 5 pounds, 5½ ounces.

Terramycin and streptomycin are the only antibiotics other than penicillin that have been investigated thus far for their antitoxic action against menstrual toxin in rats.[5] The latter, although it completely sterilized the menstrual discharge tested, offered no protection. Terramycin, although toxic in itself, prolonged survival time after lethal doses of menstrual toxin. Probably because of its toxicity the results were less striking than with penicillin, but the drug seemed worth trying in this patient who was sensitive to penicillin. When given by mouth, as in this experiment, alleviation of toxemia was less immediate than after intravenous penicillin, but the recrudescence of signs and symptoms when it was omitted and the subsequent apparent control of toxemia upon reinstituting therapy favor the conclusion that it had an antitoxic action entirely similar to that of penicillin.

Had this patient been seen at the clinic prior to her twentieth week, she would probably have been started on diethylstilbestrol, with the hope of preventing late pregnancy complications[6] which could have been predicted, considering her medical history and the finding of an elevated diastolic pressure early in pregnancy. Renal studies were not performed prior to delivery, but the urine contained finely granular and hyaline casts and the whole picture suggests that her childhood illness had left her with kidney function inadequate for the demands of pregnancy. The vascular embarrassment and tissue catabolism that would be expected to develop might have been postponed or minimized if maximum secretory activity in the production of estrogen and progesterone by the placenta had been stimulated from early in pregnancy by the prophylactic administration of stilbestrol, thereby providing maximum vascular support.

In our experience to date, stilbestrol alone, given to patients already showing signs of toxemia, has had no beneficial influence on the toxemia and has

resulted in no increase in the excretion of sodium "pregnanediol" glucuronide (NaPG).[2] When early signs of toxemia, however, were controlled by protective pseudoglobulin, a protein fraction of human exudative fluid which protects rats against menstrual toxin,[7] a few patients have responded to definitive treatment with stilbestrol by evidence of increased secretory activity of the placenta as reflected in their curves for urinary NaPG.[2] This type of therapy, started early in the course of the disease, should offer the best chance of prolonging pregnancy with a minimum amount of damage to the mother and a maximum development of the fetus. Combined therapy with penicillin and stilbestrol, therefore, was tried in the following 2 patients who were presenting signs of toxemia in the second trimester.*

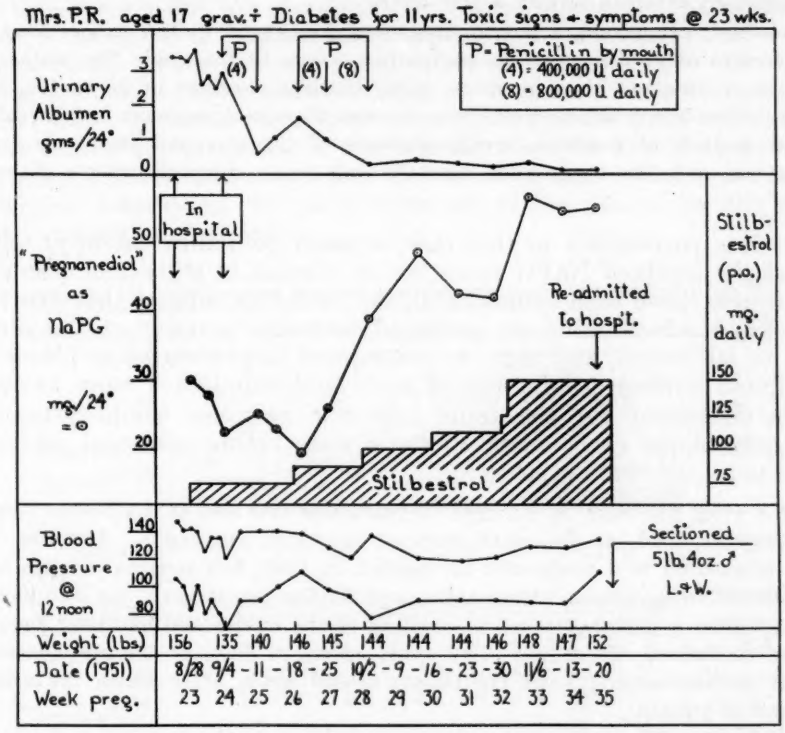

Mrs. P.R. aged 17 grav. + Diabetes for 11yrs. Toxic signs + symptoms @ 23 wks.
Urinary Albumen gms/24°
P (4)
P (4) (8)
P- Penicillin by mouth
(4) = 400,000 U daily
(8) = 800,000 U daily
"Pregnanediol" as NaPG mg/24° = ⊙
In hospital
Re-admitted to hosp't.
Stilbestrol
Stilb-estrol (p.o.) mg. daily
Blood Pressure @ 12 noon
Sectioned
5lb. 4oz. ♂
L.+W.
Weight (lbs)
156 135 140 146 145 144 144 144 146 148 147 152
Date (1951)
8/28 9/4 - 11 - 18 - 25 10/2 - 9 - 16 - 23 - 30 11/6 - 13 - 20
Week preg.
23 24 25 26 27 28 29 30 31 32 33 34 35

Fig. 7.

CASE 7 (Fig. 7).—Mrs. P. R., a 17-year-old primigravida who had had diabetes for 11 years, was admitted to the Boston Lying-in Hospital in her twenty-third week of pregnancy with nausea, vomiting, frontal headache, albuminuria, hypertension, and marked edema. During 8 days of bed rest and a salt-free diet she lost 21 pounds and became free of symptoms. Her blood pressure dropped from 146/105 to 120/70. Albuminuria, however, which was showing the typical diurnal rhythm, was not appreciably reduced, and her output of urinary NaPG was decreasing despite the fact that she had been started on oral stilbestrol. She was discharged on September 4 with instructions to continue stilbestrol according to our schedule,[6] to take 400,000 units of oral penicillin daily, and to return to the clinic twice weekly with 24-hour specimens of urine. Upon becoming ambulatory her blood pressure rose to 140/90, but the urinary albumin was markedly decreased by the end of a week

*We are indebted to E. R. Squibb & Sons for the stilbestrol used in these cases. The progesterone given to Mrs. A. A. (Case 8) was generously supplied by Schering Corporation through the kindness of Dr. Edward Henderson.

on penicillin and her excretion of NaPG had started to rise. Penicillin was then omitted for 10 days, during which time the albuminuria and diastolic pressure rose and the NaPG curve fell off again despite an increase in the dosage of stilbestrol. She was again given oral penicillin, the daily amount being increased to 800,000 units. By the end of 2 weeks albuminuria had practically disappeared, the diastolic pressure had dropped from 110 to 75 mm. Hg, and the curve for urinary NaPG was showing the rapid rise that is normal for this period of gestation. Upon discontinuing penicillin, there was no recrudescence of albuminuria and NaPG continued to rise for 10 days. A subsequent drop in the NaPG curve at 31 to 32 weeks appeared to be temporarily corrected by an increase of stilbestrol above the usual dosage schedule. NaPG excretion did not increase, however, after the thirty-third week. This observation, together with a sudden gain in weight and rise in diastolic pressure at 35 weeks, led to the decision to have her admitted for delivery, which was performed by cesarean section 2 days later.

The infant, a 5 pound, 4 ounce, male, was discharged well, 8 ounces over his birth weight, 24 days after delivery. In postpartum visits to the clinic the mother has continued to show elevated blood pressure, with diastolic readings of 90 to 100, but no albuminuria. Complete renal studies when she was 23 weeks pregnant had revealed no abnormalities or lack of function, roentgenograms of the legs had shown no evidence of arteriosclerosis, and the eyegrounds revealed only early nonproliferative diabetic retinopathy.

The close correlation in this case between penicillin therapy, the clinical signs, and the levels of NaPG excretion in relation to stilbestrol administration may, of course, have been coincidental, but certainly suggest that neutralization of the toxin made possible an increased secretory activity of the placenta in response to stilbestrol, and that the consequent improvement of placental function inhibited further production of toxin and supplied a more normal intrauterine environment for the fetus. Such a response would presumably be possible only in the early stages of the disease before placental pathology had advanced to an irreversible stage.

CASE 8 (Fig. 8).—Mrs. A. A., aged 24 years, was first seen at the Boston Lying-in Hospital on July 11, 1951, at the ninth week of her third pregnancy. Her first had spontaneously miscarried at 8 weeks and her second, in 1949, had terminated with a stillbirth at 37 weeks following edema, albuminuria, and sudden hemorrhage. In February of 1951, she had consulted a doctor because of swelling of the ankles and had been found to have albumin in the urine. There was some ankle edema in July, at the ninth week of pregnancy, but no albuminuria until the twenty-second week, after which the urine was at no time free of protein.

On November 13, at 27 weeks, she was admitted to the hospital because of sudden marked edema of the ankles, feet, and abdomen. Her blood pressure was normal and her albuminuria, although it exhibited a diurnal rhythm, was less than 1 Gm. in 24 hours. The first 2 days of bed rest and salt-free diet resulted in a 2 pound loss of weight with diuresis and disappearance of visible edema but no decrease in protein excretion. During the following 3 days albuminuria increased steadily to 1.3 Gm. in 24 hours and she again began retaining fluid. Urinary NaPG was extremely low for this period of gestation and had not increased on oral stilbestrol. Penicillin therapy was started on the sixth hospital day, a total of 5 million units being given intragluteally during the first 24 hours. A drop in urinary albumin, increase in urine output, and rise in the urinary NaPG were maintained during the following week while intramuscular injections of pencillin and oral stilbestrol were continued. Interruption of the penicillin for 5 days was accompanied by a recrudescence of albuminuria, fluid retention, edema, and a flattening out of the curve for urinary NaPG. The patient was now at home in bed and oral penicillin was tried in the hope of re-establishing a placental response to stilbestrol. This was not accomplished, although a temporary alleviation of albuminuria and fluid retention followed the daily administration of 1,600,000 units. By the end of 10 days, despite an increase in the

dosage of penicillin to 2,400,000 units daily and in that of stilbestrol to 125 mg. daily the NaPG curve was falling and albuminuria and fluid retention were increasing. Furthermore, the patient could not tolerate these large dosages of oral penicillin without nausea and vomiting. She was therefore re-admitted to the hospital for intramuscular injections of penicillin and also of progesterone, since the conclusion had been reached that placental secretory function could no longer be stimulated by stilbestrol. Five million units of intramuscular penicillin during the first 24 hours in the hospital were again followed by diuresis and decreased albuminuria. There was also a marked rise in urinary NaPG without any increase in the stilbestrol dosage and before any progesterone was given. This fact was not known, however, until after injections of progesterone had been started. Once started, we were reluctant to interrupt progesterone therapy but wish now that we had, for her metabolism of administered progesterone appeared to be quite abnormal. Even when 1 Gm. was given daily by vaginal suppository, the increment in excreted NaPG calculated as pregnanediol amounted to no more than 2 per cent of the progesterone given. In the meantime the albuminuria increased despite the fact that she was getting 3 million units of penicillin daily, the fetal heart became irregular, and she for the first time exhibited a slight elevation of blood pressure (from 110/60 to 130/84). A cesarean section was performed on December 19 when she was 32 weeks and 3 days pregnant. The 2 pound, 10 ounce, infant died 34 hours later. Autopsy revealed an extensive cerebral hemorrhage. The pediatrician was of the opinion that this was due to prematurity rather than birth injury.

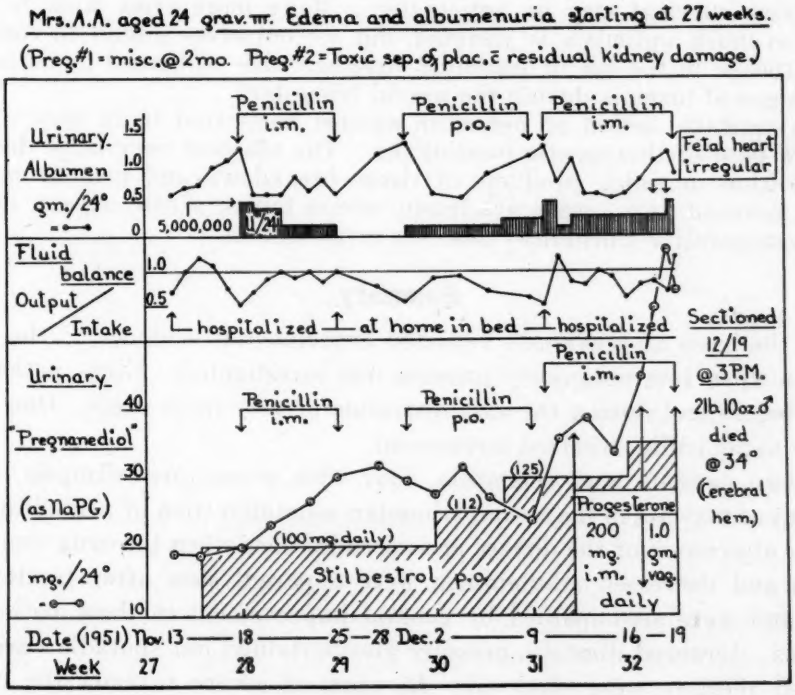



Fig. 8.

This patient has continued to excrete about 0.6 Gm. of albumin per 24 hours since delivery. It seems probable that an inherent kidney deficiency was the basis for her difficulties during this pregnancy and that penicillin lowered the albuminuria only to what might be termed her "nephritic baseline." In retrospect, we wish that we had kept her in the hospital from the start on combined therapy with oral stilbestrol and intramuscular penicillin in

amounts sufficient to control the superimposed toxemia. A more normal placental function might have been maintained and the infant carried to a greater degree of maturity.

## Comment

Just how practical penicillin will prove to be in the treatment of pre-eclampsia and eclampsia remains to be determined. In the 6 severe cases of the disease reported, it appeared to alleviate but not cure toxemia; the indication being that its action was limited to neutralization of circulating toxin with little or no effect on the rate of toxin production. Very large doses must be given. From our experience to date we would recommend starting therapy with no less than 1 million units of potassium penicillin G by intravenous injection accompanied by 1 million units intramuscularly and followed by the same amount by intramuscular or intravenous injection at no more than 2-hour intervals. How long this should be continued would depend upon the response, but, regardless of clinical improvement, the fact that the infant's life is still in jeopardy must constantly be borne in mind. Interruption of pregnancy remains the only "cure" for toxemia, but, in the critically ill patient, penicillin might make this a safer procedure than it would be otherwise.

The use of penicillin in the treatment of early signs, as reported in the last two cases of this series, offers an appealing attack on the difficult problem of maintaining pregnancy until fetal development has reached a stage at which extrauterine survival may be anticipated. Many more cases must be studied before too much optimism is justified, but we ourselves intend to concentrate future studies on the use of penicillin together with stilbestrol in patients presenting signs of toxemia during the second trimester.

The antitoxic action of penicillin against menstrual toxin may well open up a new field of therapeutic possibilities. The effect of very large doses upon any condition in which products of tissue breakdown and protein catabolism may be involved (e.g., crush syndrome, severe burns, shock, oxygen deficiency states, postoperative morbidity) deserves investigation.

## Summary

On the basis of previously reported experimental evidence,[3, 5] the effect of penicillin upon late pregnancy toxemia was investigated. Eight patients were studied before and during the administration of very large doses. One of them, sensitive to penicillin, received terramycin.

In two patients with eclampsia, four with severe pre-eclampsia, and two with signs of toxemia in the second trimester, administration of penicillin was followed by alleviation of the disease and recrudescence when the drug was omitted. Diuresis and decreased albuminuria were apparent soon after treatment was started and were accompanied by general improvement in those patients with symptoms. Lowered diastolic pressure also pertained but sporadic rises despite continued therapy were observed. In cases of severe toxemia the beneficial action of penicillin appeared to be limited to the mother, since intrauterine death despite control of toxemia occurred in two of six such patients studied.

In the two patients presenting signs of toxemia in the second trimester, penicillin was given in conjunction with stilbestrol. As is usual in toxic patients treated definitively, stilbestrol alone caused no increase in the excretion of sodium pregnanediol glucuronide (NaPG). When penicillin was also given, in sufficient dosages to control signs of toxemia, the curve for urinary NaPG rose.

Despite the fact that one of the infants died of prematurity after section, this type of therapy appears to offer promising possibilities for the fetus as well as the mother.

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# THE CAUSE AND PREVENTION OF DIFFICULT LABOUR*

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A NORMAL labour for the purposes of this paper is defined as one in which the vertex presents and which is completed in 24 hours or less by spontaneous delivery without injury or undue discomfort to the mother. It is safe to say that this ideal can never be attained in all cases. Abnormal labour will always exist, but a better understanding of the many causes which contribute to it will lead to better treatment.

If it were possible to define difficult labour precisely, its incidence could be estimated and the relative importance of the various causative factors more easily seen. Estimates have been based on the duration of labour, the incidence of instrumental delivery, puerperal morbidity, and foetal and maternal death rates, but none is entirely satisfactory. Denman in 1798 wrote, "Every labour in which the head of the child presents which is protracted beyond 24 hours shall be called difficult." There are, of course, labours lasting much less than 24 hours which are very abnormal and there are others lasting much longer than 24 hours where the pains are irregular or weak for many hours, but where the labour progresses quickly and smoothly in the end.

The operative delivery rate is unsatisfactory because of different customs with regard to the use of forceps. It would be difficult to compare the incidence of difficult labour in the United States and Holland on this basis. Stillbirth rates cannot be used either, since 3 out 4 stillbirths are related to conditions pre-existing in the mother and not to the hazards of birth. Even in cases of difficult labour where birth trauma might be expected, the vitality of the child, dependent largely on the mother's health during the pregnancy, has a bearing on the chance of his surviving the stress of labour.

Another difficulty is the lack of careful records of labour. Careful and detailed records are, of course, to be found in many maternity hospitals, but, in Britain at least, because of the methods of selection of patients for hospital confinement, even "booked cases" contain an undue proportion of abnormal and difficult cases. Again, in large cities, one hospital may be in a prosperous residential area where patients are relatively healthy and emergency cases few; another may be in a district where many are in poor physical condition and where emergency cases form a relatively large proportion of the admissions. Great care must therefore be taken in coming to conclusions about the frequency of abnormalities or in comparing the results of treatment between one hospital and another.

*The Joseph Baer Lecture, delivered, by invitation, at a meeting of the Chicago Gynecological Society, Oct. 18, 1951.

Accurate regional statistics are needed. The figures used in this paper are derived chiefly from the records of the Aberdeen Maternity Hospital, which is the only maternity hospital in the city and deals with 85 per cent of all primiparas, and it has been possible to obtain detailed records of the other 15 per cent of births occurring in a private nursing home or in the patient's home, so that the problems of sampling do not arise.

## Factors Affecting the Course of Labour

As is well known, the course of labour is influenced by three main factors: (a) the efficiency of uterine contractions and the voluntary expulsive efforts, (b) the size and the position of the child, and (c) the shape and size of the pelvis.

In some cases a fault in one of these, such as a severely contracted pelvis, may be the single obvious cause of difficulty in labour, while in others all three factors play a part, and it may be very difficult to determine their relative importance.

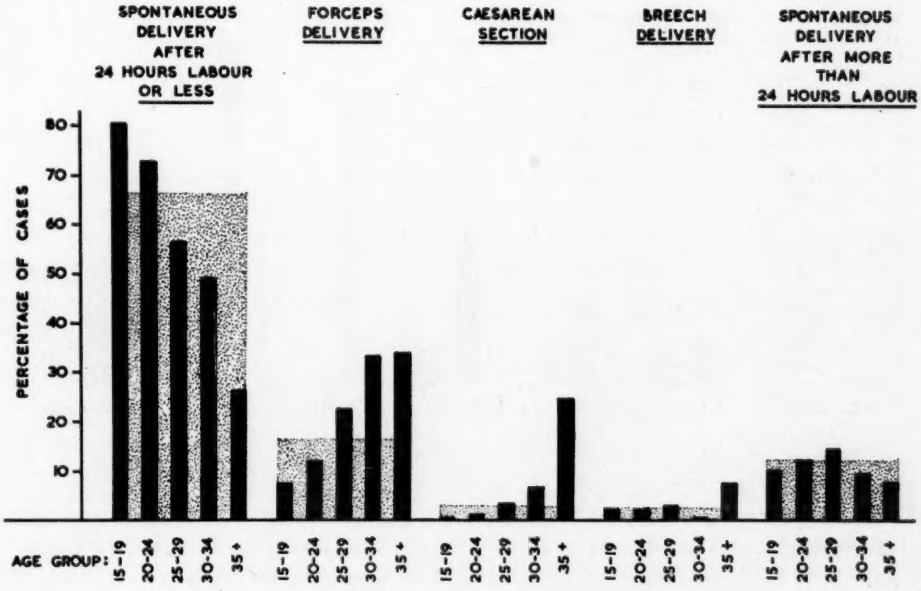


Fig. 1.

For the purpose of this study it has been necessary to place each case in one category. If there was any suspicion of disproportion the difficulty was held to be due to contracted pelvis. If there was no disproportion but an occipitoposterior position was diagnosed during labour, the difficulty was ascribed to this. All the others have been labelled "dysfunction," except where such conditions as foetal or maternal distress made it necessary to terminate the labour at once, and these cases have been placed in the group "other conditions." All breech and other abnormal presentations have been excluded from the present study.

It will be seen that this method of classification underestimates the amount of abnormal labour due to dysfunction, since even when there is disproportion

or an occipitoposterior position poor contractions may be the factor most responsible for the difficult labour. It is possible, of course, that in some cases the uterine inertia is secondary to the disproportion or the occipitoposterior position.

*The Influence of Age.—*

Fig. 1 shows the type of labour in relation to the age of the patient in a series of 1,792 "booked" married primiparas in the Aberdeen Maternity Hospital in the year 1949-1950. The incidence of spontaneous delivery in less than 24 hours fell from 80.3 per cent in the 15 to 19 year age group to 26.1 per cent in the age group 35 years and over. Conversely, the incidence of labour lasting longer than 48 hours rose from 2 per cent in the youngest age group to 8 per cent in the oldest. The forceps delivery rate rose steeply from 7 per cent in the youngest age group to 36 per cent in those of 35 and over.

There is no doubt, therefore, on the basis of these figures, that labour is most normal in the age group 15 to 19 years and that even in the age group 20 to 24 years a definite deterioration in performance is evident.

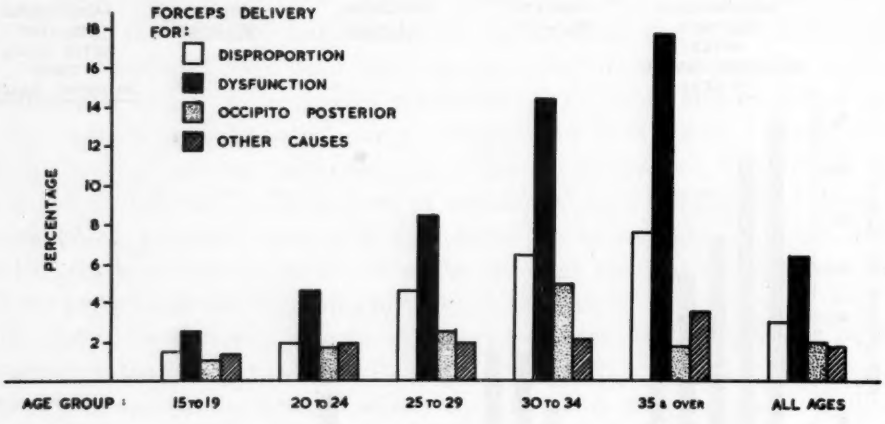


Fig. 2.

Fig. 2 gives an analysis by age of the indications for the use of forceps. It shows that the increase in the forceps delivery rate with age was due largely to an increase in dysfunction, that is to say, due either to faulty uterine action or to poor expulsive efforts and rigidity of the pelvic floor or to a combination of all of these. An increase in the incidence of contracted pelvis and occipitoposterior position is unlikely to occur with age so that the increase in the forceps rate attributed to these conditions is probably to be explained largely by the poor uterine contractions and ineffectual bearing down effects which increase greatly with age.

Fig. 3 gives the incidence of intact perinaeum after spontaneous vertex delivery and it shows that in the age group 15 to 19 years the perinaeum remained intact in 55 per cent of cases and that even by the age group 20 to 24 years this percentage had fallen to 36 per cent. The routine management of labour was conservative, in that episiotomy was performed only when it seemed clear that tearing would occur or where the progress was held up by a rigid perinaeum.

It will be noted that less than 20 per cent of primiparas in the age group 30 to 34 years, who were able to deliver the child unaided, had intact perinaea.

This seems a surprisingly low figure when it is remembered that 40 per cent of the total primiparas in this age group were delivered either by forceps or caesarean section. It seems, therefore, that only about 12 per cent of the women in this age group are capable of a completely "normal" labour, that is, spontaneous delivery with an intact perinaeum. The rise, seen in Fig. 3, in the incidence of intact perinaeum in the age group 35 years and over is probably a chance variation due to the very small number of cases in that group.

Fig. 1 shows that the caesarean section rate rises steadily with age from 0.4 per cent in the age group 15 to 19 years to 24.6 per cent in those 35 years of age or older. The greatly increased incidence in the 35+ age group is due partly to the fact that in elderly primiparas caesarean section is performed early in labour or even before the onset of labour in some circumstances to ensure a live child rather than because labour is difficult.

The evidence, therefore, based on the incidence of intact perinaeum after spontaneous delivery, forceps delivery, and caesarean section suggests that in primigravidas labour is much easier and more "normal" between the ages of 15 and 19 years than at any other age and that the incidence of abnormal labour increases steadily with age.

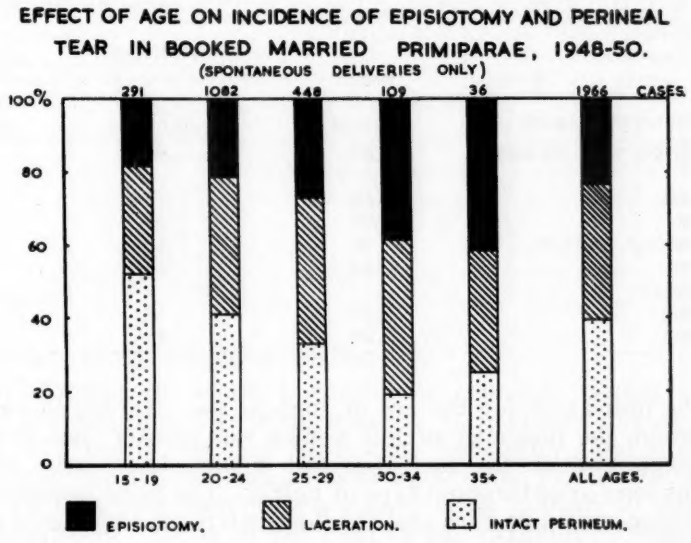


Fig. 3.

*Influence of Parity.*—

It is well known that the second labour is often easy when the first has been difficult. Table I shows that the incidence of forceps delivery in first and second labours in booked hospital cases was 13.36 and 2.03 per cent, respectively. The decrease was greatest in the dysfunction group and least where there had been disproportion in the first labour. The caesarean section rates in first and second labours were 1.81 and 1.59 per cent, respectively. The decrease in the incidence of caesarean section was much less, partly because those who were delivered by caesarean section the first time would always be admitted to hospital the second time, and also because most of the caesarean sections in primigravidas were performed for disproportion due to contracted pelvis, which, if severe enough, to require caesarean section in the first labour, would usually necessitate it also in a second labour.

TABLE I. FORCEPS DELIVERIES IN FIRST AND SECOND LABOURS BY CAUSE

| REASON FOR FORCEPS | RATE PER 100 FIRST LABOURS | RATE PER 100 SECOND LABOURS | RATE IN SECOND LABOURS AS PERCENTAGE OF RATE IN FIRST LABOURS |
|---|---|---|---|
| Contracted pelvis, disproportion | 2.97 | 0.71 | 23.9 |
| Dysfunction | 6.52 | 0.48 | 7.4 |
| Occipitoposterior presentation | 2.01 | 0.36 | 17.9 |
| Others | 1.86 | 0.48 | 25.8 |
| All causes | 13.36 | 2.03 | 15.2 |

*Influence of Height.—*

Table II shows the height distribution in relationship to the type of difficult labour and the method of delivery in primigravidas.

The group "Spontaneous delivery over 24 hours" shows the same height distribution as that for all patients at risk; that is to say, about 25 per cent under 5 feet, 1 inch, and 25 per cent of 5 feet, 4 inches, or over, 50 per cent between 5 feet, 1 inch and 5 feet, 4 inches.

TABLE II. TYPE OF DIFFICULT LABOUR IN PRIMIPARAS BY HEIGHT

| TYPE OF DIFFICULT LABOUR | PERCENTAGE | | |
|---|---|---|---|
| | SHORT (UNDER 5 FEET, 1 INCH) | MEDIUM | TALL (5 FEET, 4 INCHES AND OVER) |
| Spontaneous delivery over 24 hours | 24 | 50 | 26 |
| *Forceps.—* | | | |
| Disproportion | *44* | *47* | *9* |
| Dysfunction | 20 | 58 | 22 |
| Occipitoposterior position | 19 | 46 | 35 |
| Other causes | 34 | 43 | 23 |
| *Caesarean Section.—* | | | |
| Disproportion | *83* | *12* | *5* |
| Other causes | 26 | 48 | 26 |

Where the indication for the use of forceps was dysfunction and occipitoposterior position, the incidence of tall women was greater than average. This is probably explained by the fact that tall women have large pelves and a tendency to the long or anthropoid type of pelvis. The large measurements mean that disproportion would be rare and the long pelvis predisposes to the occipitoposterior position, but neither the large size nor the shape of the pelvis would influence the incidence of dysfunction which we have shown to depend largely on the age of the patient.

TABLE III. TYPE OF SECOND LABOUR BY HEIGHT AND BY REASON FOR FORCEPS IN FIRST LABOUR (PERCENTAGES IN PARENTHESES)

| FIRST LABOUR REASON FOR FORCEPS | SECOND LABOUR TYPE OF DELIVERY | SHORT (UNDER 5 FEET, 1 INCH) | MEDIUM | TALL (5 FEET, 4 INCHES AND OVER) | ALL HEIGHTS |
|---|---|---|---|---|---|
| Disproportion | Spontaneous | 25 | 28 | 3 | 56 (76) |
| | Forceps | 4 | 6 | – | 10 (13) |
| | Caesarean | 4 | 3 | 1 | 8 (11) |
| | All types | 33 (45) | 37 (50) | 4 (5) | 74 (100) |
| Others | Spontaneous | 43 | 127 | 41 | 211 (94) |
| | Forceps | 3 | 6 | 2 | 11 (5) |
| | Caesarean | – | 1 | 1 | 2 (1) |
| | All types | 46 (20) | 134 (60) | 44 (20) | 224 (100) |

Where forceps were required for disproportion, 44 per cent were small (under 5 feet, 1 inch) and when caesarean section was necessary for the same reason 83 per cent were small.

Table III gives the result of the second labour where the first was terminated by forceps. It shows that forceps or caesarean section were necessary in a second labour in 24 per cent of the cases where forceps had been necessary in the first labour for disproportion. Only one of the eighteen patients in the group was tall. Only 6 per cent of those who had forceps in the first labour for causes other than disproportion had forceps or caesarean section the next time.

Table IV shows that of 23 patients who had caesarean section performed for disproportion in the first labour 16 had a second caesarean section and 4 had forceps delivery. Twenty of the twenty-three patients were small.

A practical application of these findings is that very few women of 5 feet, 4 inches, or over have disproportion requiring caesarean section and tall women almost without exception have a spontaneous delivery in the second labour if the first has terminated in a vaginal delivery.

TABLE IV. TYPE OF SECOND LABOUR BY HEIGHT AND BY REASON FOR CESAREAN SECTION IN FIRST LABOUR

| FIRST LABOUR REASON FOR SECTION | SECOND LABOUR TYPE OF DELIVERY | SHORT (UNDER 5 FEET, 1 INCH) | MEDIUM | TALL (5 FEET, 4 INCHES AND OVER) | ALL HEIGHTS |
|---|---|---|---|---|---|
| Disproportion | Spontaneous | 3 | – | – | 3 |
| | Forceps | 2 | 1 | 1 | 4 |
| | Caesarean | 15 | 1 | – | 16 |
| | All types | 20 | 2 | 1 | 23 |
| Others | Spontaneous | – | – | 2 | 2 |
| | Forceps | – | 1 | – | 1 |
| | Caesarean | – | – | 1 | 1 |
| | All types | – | 1 | 3 | 4 |

*Influence of Good Social Circumstances.—*

The environment in which a woman is brought up has an important influence on her reproductive performance. It not only affects her physical development and health but her behaviour, knowledge, and ability to cope. It also influences her attitude to childbearing and the age at which she has her first child. To illustrate these points I have made a study of two contrasting groups in Aberdeen: 10 to 15 per cent of the primiparas who paid for the confinement in a private Nursing Home, and the 85 per cent for whom the medical attention and hospital accommodation were free.

The private patients look much healthier on the whole than those in hospital and they are certainly taller. For example, the percentage of the total private and hospital patients who were small (under 5 feet, 1 inch) was 5 and 25 per cent, respectively. The private patient was on the average about 5 years older than the hospital patient at the time of the birth of the first child.

Tables V and VI shows the caesarean rates in the two groups by age and height. In both groups caesarean section rates increase with age and decrease as height increases. It is very seldom performed in those who are young and tall. The total caesarean section rate is relatively high in the private patients largely because of the unfavourable age distribution. Fig. 4 shows that the forceps rate is higher at all ages in the private patients than in the hospital patients in both periods under review. (The decline in the forceps and caesarean section rates in the private group in the postwar years will be discussed later.) Since the private patients are taller and have bigger pelves than the hospital patients, it is clear that, even if the factors of age and height are allowed

for, some relationship still remains between social class and the proportion of "normal" labours (spontaneous delivery in less than 24 hours). There are several possible reasons for this, some of which are easily explained and others more complex.

TABLE V. CAESAREAN SECTION RATES AMONG 1,401 PRIVATE NURSING HOME PRIMIPARAS

| AGE (YEARS) | SHORT (UNDER 5 FEET, 1 INCH) | MEDIUM | TALL (5 FEET, 4 INCHES AND OVER) | ALL HEIGHTS |
|---|---|---|---|---|
| 15-19 | – | – (1) | – (8) | – (9) |
| 20-24 | – (17) | 1.9 (101) | 0.6 (172) | 1.0 (290) |
| 25-29 | 18.7 (32) | 5.2 (189) | 0.7 (304) | 2.5 (525) |
| 30 and over | 13.1 (38) | 6.1 (213) | 3.9 (326) | 5.4 (577) |
| All ages | 12.6 (87) | 4.9 (504) | 1.9 (810) | 3.3 (1,401) |

TABLE VI. CAESAREAN SECTION RATES BY MATERNAL AGE AND HEIGHT (3,600 BOOKED PRIMIPARAS, ABERDEEN MATERNITY HOSPITAL)

| AGE (YEARS) | SHORT (UNDER 5 FEET, 1 INCH) | MEDIUM | TALL (5 FEET, 4 INCHES AND OVER) | ALL HEIGHTS |
|---|---|---|---|---|
| 15-19 | 1.4 (137) | – (199) | – (79) | 0.4 (415) |
| 20-24 | 1.3 (433) | 0.1 (864) | – (396) | 0.4 (1,693) |
| 25-29 | 3.5 (226) | 0.9 (444) | 0.8 (243) | 1.5 (913) |
| 30+ | 5.2 (152) | 4.1 (294) | 3.0 (133) | 4.3 (579) |
| | 2.5 (948) | 0.9 (1,801) | 0.8 (851) | 1.3 (3,600) |

*Demand for Relief of Pain.*—In general, women of better economic status seek more relief from the pain of labour and are less inclined than those from the lower income group to accept suffering as inevitable. The attitude toward natural childbirth has, however, changed perceptibly in the last few years and it is fortunate that well-educated and imaginative women, who formerly were more concerned with relief of pain, have shown the greatest interest in the healthier attitude.

The attitude of the doctor or midwife is also important. Fig. 4 already referred to gives the incidence of forceps deliveries and caesarean section in primigravidas in private practice in two periods, 1942 to 1945 and 1946 to 1948, contrasted with the Maternity Hospital for the years 1941 to 1945. It shows a fall of 20 per cent in the incidence of forceps delivery at all ages in the private patients during the period, and more detailed analysis year by year showed that the change occurred suddenly in 1946. This coincided with the return of the Matron of the Nursing Home from war service. She was not only a first-class midwife, but a woman of great personality and the change is probably a measure of her ability to inspire the patients to make the effort necessary for natural childbirth.

*Greater Concern About the Child.*—The size of the family nowadays tends to be carefully planned and the total limited to two or three children. Concern for the individual child becomes proportionately greater. Parents are less willing to accept as unavoidable the loss of a first child, and are also aware of the risks of permanent damage from asphyxia or cerebral injury in a child who survives a difficult delivery. Undue apprehension about the outcome of labour may upset uterine action so that in some cases caesarean section may be necessary; the doctor may also become overanxious about the possible risks to the baby and have recourse too frequently to caesarean section. There is, of course, considerable cause for anxiety, since the foetal mortality rises steeply with age, especially after 30 years, and a relatively high proportion of those

in the higher income groups, who are inclined to worry most, are in the older age groups.

*Career Women.*—Many women who postpone marriage and childbearing till the thirties have difficulty in making the change from professional interests to purely domestic ones and some conflict may remain after decisions have been taken. It may be that the woman who has her first child at 30 is quite a different type from the woman who begins her reproductive life at 20. Inherent psychological and physical characteristics may exist.

The possible influence of the emotions on uterine action in labour is still poorly understood. There seems little constant and obvious interrelationship since many patients who are tense and anxious (or have good reason to be) have easy labours and some who are outwardly placid and relaxed develop severe dysfunction. Possibly some cases of disordered uterine action may be caused by emotional tension at a subconscious level, which is not evident to the casual observer nor appreciated by the patient herself. The effect, if any, of emotional factors on uterine action will be established only if psychiatrists and obstetricians working together are able to show that dysfunction can be predicted by means of a knowledge of significant emotional malajustment. When there is a long interval between maturity and the first pregnancy there appears to be a lessening of reproductive efficiency. Not only is the labour often prolonged and difficult, with increased risk to the mother and child, but there is also a much greater risk of death of the foetus just before or during the early stages of labour, probably as a result of placental insufficiency.

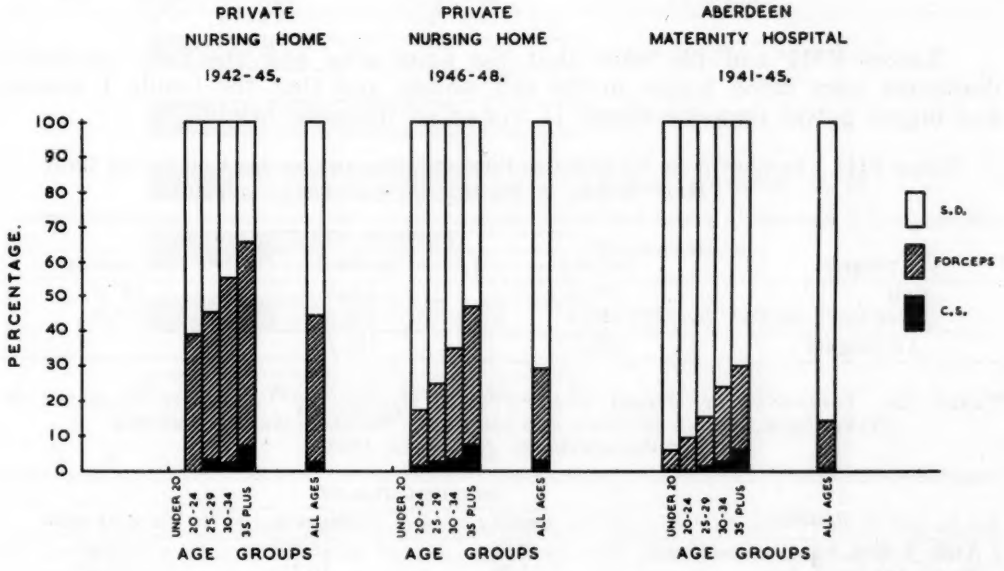


Fig. 4.

*Influence of Poor Social Circumstances.*—

*Influence on Physique.*—It has already been shown that hospital patients are younger and smaller than private patients and that forceps delivery and caesarean section because of disproportion are confined to small or medium-sized women. Fig. 5 shows the percentage of Aberdeen primigravidas arranged by height and the social class of the father. The social classification is that used by the Registrar General, Class I being the upper professional and business class and Class V consisting of unskilled labour. It shows that the proportion

of small women increases and the proportion of tall women decreases as the social class falls.

Bernard (1952) has studied the relationship between height and physical health and the shape and size of the pelvis. Two groups of 100 patients, one under 5 feet and the other 5 feet, 5 inches or over, were examined clinically and placed in Grades I and II depending on whether they were judged to be of good physique and in good health or the reverse. The pelvic shape and size were then studied by x-ray pelvimetry.

Table VII shows that the tall women had pelves which were mostly round or long and very few flat, while the small women had a high proportion of flat pelves. At both heights there was more flattening in the Grade II women. This confirms and amplifies the observations of Thoms, published many years ago, that the "normal" pelvis is either round or slightly long and that flattening of the pelvic brim is due to malnutrition.

TABLE VII. PERCENTAGE DISTRIBUTIONS OF PELVIC BRIM SHAPES (NICHOLSON'S CLASSIFICATION) BY MATERNAL HEIGHT AND PHYSICAL GRADING (BERNARD, 1952)

| HEIGHT | GRADE | ROUND OR LONG OVAL | FLAT OR TRIANGULAR | ALL SHAPES |
|---|---|---|---|---|
| *Tall.*— | | | | |
| | Grade I | 94.8 | 5.2 | 100 |
| | Grade II | 87.5 | 12.5 | 100 |
| *Small.*— | | | | |
| | Grade I | 73.6 | 26.4 | 100 |
| | Grade II | 63.0 | 37.0 | 100 |

Tables VIII and IX show that the brim area and the true conjugate diameters were much larger in the tall women and that the Grade I women had bigger pelves than the Grade II women of the same height.

TABLE VIII. INFLUENCE OF HEIGHT AND PHYSICAL GRADING ON AREA OF PELVIC BRIM (MEAN AREAS IN SQUARE CENTIMETERS)

| HEIGHT | PHYSICAL HEALTH | | |
|---|---|---|---|
| | GRADE I | GRADE II | ALL GRADES |
| Tall | 138.5 | 134.2 | 137.6 |
| Small | 109.9 | 106.0 | 106.8 |
| All heights | 123.7 | 120.1 | |

TABLE IX. INFLUENCE OF HEIGHT AND PHYSICAL GRADING ON CONJUGATE DIAMETER OF PELVIC BRIM, AMONG 100 TALL AND 100 SMALL WOMEN (MEAN DIAMETERS IN CENTIMETERS) (BERNARD, 1952)

| HEIGHT | PHYSICAL HEALTH | | ALL GRADES |
|---|---|---|---|
| | GRADE I | GRADE II | |
| Tall (5 feet, 5 inches and over) | 12.80 | 12.33 | 12.69 |
| Small (under 5 feet) | 11.01 | 10.71 | 10.77 |
| All heights | 11.90 | 11.52 | |

TABLE X. PERCENTAGE DISTRIBUTION OF PELVIC BRIM SHAPES (NICHOLSON'S CLASSIFICATION) BY HEIGHT AND PHYSICAL GRADING, IN MALES (BERNARD, 1952)

| HEIGHT | GRADE | ROUND OR LONG OVAL | FLAT OR TRIANGULAR | ALL SHAPES |
|---|---|---|---|---|
| *Tall.*— | | | | |
| | Grade I | 90.0 | 10.0 | 100 |
| | Grade II | 77.8 | 22.2 | 100 |
| *Small.*— | | | | |
| | Grade I | 72.0 | 28.0 | 100 |
| | Grade II | 45.0 | 55.0 | 100 |

Table X shows the findings in an investigation which was carried out in a group of tall and small men. The tall men (medical students) had pelvic brims of the same shape as the tall women—again confirming the findings of Thoms—and the small men had the same type of flatening of the pelvic brim as the small women (compare with Table VII).

This suggests very strongly that the so-called android pelvis is not a "male" type and is not due to an endocrine influence but is really the result of malnutrition. It seems clear that tall women have a brim area large enough to take a baby of almost any size and at the same time a pelvis of good shape. This means that disproportion is practically nonexistent in tall women and even if the position is an occipitoposterior, labour will be easy provided pains are good. It has been shown that uterine dysfunction is very much influenced by the age of the patient and is very seldom encountered in primigravidas under 20 years of age. In such cases slight delay on the pelvic floor may occur due to rigid muscles or the lack of ability of the head to extend round the pubis as in the occipitoanterior position. In a second labour, the pelvic floor having been stretched, labour will be short and easy. In the lower economic groups, although most primigravidas are young, few of them are tall, and therefore difficult labour does occur despite their youth.

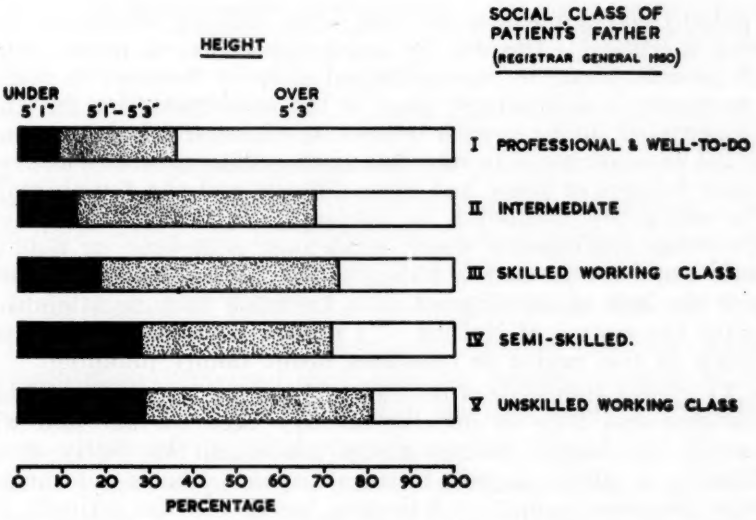


Fig. 5.

In women of intermediate height much will depend on the size of the child. If the child is of average size vaginal delivery will usually be possible, but with a large child (9 pounds or so) disproportion may occur, there not being the reserve of pelvic capacity available as in the tall women.

Small women of under 5 feet, 1 inch, frequently have small pelves. In our experience 20 per cent have a true conjugate diameter of under 10.2 cm. so that even with a small baby caesarean section for disproportion is frequently necessary. In our experience 15 per cent of women with a conjugate measurement of under 10.2 cm. require caesarean section.

*Influence on Attitude.*—Many of those in the lower economic groups, especially those who marry when they are young, do not seem to have the same anxiety about labour as the private patients, even if they have had a long and difficult labour. Sometimes the obstetric histories are remarkable:

*Mrs. C.*, married in 1932 at the age of 22 years.
*Obstetric History:*
1933. Difficult forceps delivery at home after 48 hours' labour; child alive.
1934. Difficult forceps delivery at home after 48 hours' labour; child alive.
1936. Difficult forceps delivery at home after 48 hours' labour; child alive.
1940. Admitted to hospital, having been in labour for 72 hours; breech presentation; delivery easy but child stillborn.
Weight of child, 8 pounds, 14 ounces.
Height of patient, 5 feet, 3 inches.
X-ray examination showed a flat pelvis.
True conjugate, 3.5 inches (8.75 cm.)
Transverse of brim, 5.4 inches (13.5 cm.)
Brim index, 64 per cent.
Brim area, 95 sq. cm.
1941. Admitted in exhausted condition, having been in labour for 3 days and 21 hours; forceps delivery of a live child, weighing 9 pounds, 6 ounces, who did well.
1942. Spontaneous delivery at home after prolonged labour due to poor pains; child alive, weight 8 pounds, 5 ounces.
1944. Booked for hospital; during pregnancy presentation sometimes breech, sometimes shoulder. Membranes ruptured early; breech presenting; caesarean section and ligation of tubes; child weighed 7 pounds, 4 ounces, alive, and did well.
1949. Interviewed; feeling well and very glad she was sterilized.

This patient married young and had seven difficult labours in eleven years before being sterilized. Despite the markedly flattened pelvic brim, a child weighing 9 pounds, 6 ounces, was delivered alive by forceps; in many of these cases the prognosis is surprisingly good if the anteroposterior flattening of the brim is compensated for by a wide transverse diameter. It is amazing that the patient should have arranged to have her sixth confinement at home even though the first three labours at home had been difficult and the fourth and fifth had resulted in emergency admission to hospital. It is hard to believe that a woman of average intelligence would make such a decision or that the family doctor would acquiesce in such a policy of drift. In some cases the reason is not so much the lack of intelligence as a tradition that no attempt should be made to alter the course of Nature. "I expect I will have my number" is a frequent reply in this region to questions about family planning.

Table XI gives a summary of the effect of age, parity, and social background on the incidence and type of difficult labour. Age for age and within each parity those in the higher income group are much less likely to experience serious difficulty in labour, largely because disproportion is uncommon amongst them. There are more operative deliveries because of the attitude factor. So many of them postpone the first birth till the age when severe uterine dysfunction is common, that long labour is frequent and the caesarean section rate high. Despite this, the foetal mortality is less than in the lower income groups because of the low prematurity rate and the superior vitality of the infants.

## Conclusions

It is clear that the frequency and types of difficult labour are influenced by the type of society under consideration. Changes in social condition may produce great changes in obstetric practice and it is important that the obstetrician should have a clear understanding of these wider influences if he is to have a balanced outlook on obstetrics and avoid drawing wrong conclusions from a too restricted study of his subject.

The fall in the number of deaths from difficult labour, which is part of the striking fall in maternal mortality which has occurred in the last fifteen years,

TABLE XI. THE EFFECT OF AGE, PARITY, AND SOCIAL BACKGROUND ON THE INCIDENCE AND TYPE OF DIFFICULT LABOUR

| FACTORS AFFECTING COURSE OF LABOUR | HIGHER INCOME GROUPS, WELL EDUCATED | LOWER INCOME GROUPS, ILL EDUCATED |
|---|---|---|
| *Age.—* | *Later Childbearing* | *Early Childbearing* |
| | 1. More dysfunction | 1. Less dysfunction |
| | 2. Fewer spontaneous deliveries | 2. More spontaneous deliveries |
| *Parity.—* | *Smaller Planned Families* | *Larger Unplanned Families* |
| | 1. More first births (more difficult labours) | 1. Few first births (fewer difficult labours) |
| | 2. Fewer serious complications of high parity | 2. More serious complications of high parity |
| *Height.—* | *Tall, Better Physique and Health* | *Short, Poorer Physique and Health* |
| | 1. Less contracted pelvis (less difficult labour from mechanical causes) | 1. More contracted pelvis (more difficult labour from mechanical causes) |
| *Attitude.—* | *More Fear of Difficult Labour* | *Less Fear of Difficult Labour* |
| | 1. Fewer spontaneous deliveries | 1. More spontaneous deliveries |
| | 2. More operative interference for relatively slight cause | 2. Less operative interference for relatively slight cause |
| | 3. End of childbearing more often determined by difficult labour | 3. Less effect of difficult labour on size of family |

is probably due rather to the more efficient treatment of difficult labour than to a reduction in its total incidence. Changes in social conditions, customs, and attitudes to childbearing may be altering the type of difficult labour rather than reducing its total incidence. For example, the improved standard of health and physique of the women of Britain is resulting in fewer difficult labours from disproportion and since there are fewer large families there are fewer cases of shoulder presentation, prolapsed cord, placenta praevia, rupture of the uterus, and other complications of high parity. But this also means that first births form a higher proportion of the total, thus increasing the proportion of difficult labours due to dysfunction; this would be increased further by any increased tendency for women to have the first child after the age of 25 years.

It is to be expected that differences in reproductive performance between women of the upper and lower economic classes will gradually decrease. The well-off and better educated women seem more aware of the advantages of natural childbirth and of the disadvantages of deferring pregnancy past the optimum age. The improved social condition of the lower income groups should show itself in better health and physical development and, as a result, less obstructed labour. There is also a clearer realisation of the disadvantages of having more children than can be clothed and fed.

Since environmental changes occur slowly and since the best results will be obtained only when the mother is reared in a good environment from birth and well fed, not only during pregnancy but during all the years from birth to maturity, there is still a great deal to be done to remove the deleterious physical effects of a poor environment. Some countries, such as Sweden, have almost

succeeded in eliminating poverty and malnutrition as a direct or indirect cause of foetal death. It is disconcerting to learn that in Sweden the birth rate has been below replacement level for many years and that the divorce and suicide rates are high, suggesting psychological instability and possibly a lack of faith in the future. These countries striving to eliminate the obvious wastage of lives and health due to malnutrition and ignorance must give careful thought to the danger which may accompany a high standard of living.

I wish to acknowledge the help received from the Director and staff of the Social Medicine Research Unit, Medical Research Council (Great Britain) in some of the research dealt with in this paper.

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# A TEST FOR PREGNANCY BASED ON THE HISTAMINOLYTIC ACTIVITY OF SERUM*

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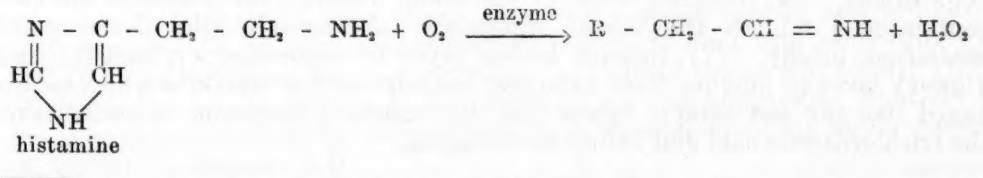
MOST of the clinical methods used today to determine pregnancy depend upon the reactions of laboratory animals to chorionic gonadotropin found in both the blood and urine of pregnant women, e.g., Friedman test (Mann, Meranze, and Golub, 1933), frog tests (Robbins and Parker, 1948, Haskins and Sherman, 1951). The purpose of this paper is to present a test for pregnancy which does not involve the use of laboratory animals and which is easy to perform. It is not as accurate from the fifth to the eighth week after the last menstrual period as the tests now in general use, but is more accurate than these after four months of pregnancy.

The test depends upon the ability of the plasma of pregnant women to destroy added histamine. This histaminolytic activity was first noted by Marcou, Athanasiu-Vergu, Chiricéanu, Cosma, Gingold, and Parhon (1938), who found it in the blood from the uterine cavity during delivery and the first few hours post partum. They also found activity in the recently delivered placenta. Since then the active principle, an enzyme known as histaminase or diamine oxidase, has been studied during pregnancy by Werle and Effkemann (1940), Zeller and Birkhäuser (1940), Zeller (1941), Ahlmark (1944), Kapeller-Adler (1944, 1951), Anrep, Barsoum, and Ibrahim (1947), and Wicksell (1949). Men and nonpregnant women have only minute amounts of this enzyme in their blood. The amount of the enzyme, as indicated by the histaminolytic activity, increases as much as a thousand fold during pregnancy and falls very rapidly after delivery. When measured by one of the less sensitive methods, the activity is reported as normal about 4 days post partum (Kapeller-Adler, 1951); with more sensitive methods it has been found to take about two weeks for a return to normal (Ahlmark). Ahlmark found that the human placenta contains high histaminolytic activity; this is presumed to be the source of the plasma histaminase.

According to Zeller (1938) the basic reaction catalyzed by the enzyme is:

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**Jackson Johnson Research Fellow of the School of Medicine.

The imine immediately hydrolyzes nonenzymatically:

$$R - CH_2 - CH = NH + H_2O \longrightarrow RCH_2 - CHO + NH_3$$

Some of the methods which have been used to determine the histaminolytic activity of serum have been colorimetric. However, the most sensitive have involved the measurement of the undestroyed histamine on atropinized guinea pig ileum (Ahlmark, Wicksell). Kapeller-Adler (1951) presents a colorimetric method based on hydrogen peroxide formation which although more sensitive than earlier colorimetric methods (e.g., Zeller, 1941) is less sensitive than the 2, 4-dinitrofluorobenzene (DNFB) method described in this paper. This DNFB method combines the sensitivity of the guinea pig ileum with the ease and convenience of a colorimetric method.

## Method

The basis of this method is the incubation of serum with a known amount of histamine, followed by the measurement of the remaining histamine by coupling with DNFB. McIntire, White, and Sproull (1950) were the first to use this reagent for histamine determination; a modification of the method developed by Graham, Lowry, and Harris was used for this work. Two forms of carrying out the pregnancy test are presented below, one qualitative and the other quantitative. The qualitative form is rapid and easy to perform; the results can be read by eye. It is not as sensitive as the quantitative test which involves the use of a Beckman spectrophotometer.

## Qualitative Test

*Apparatus.*—Test tubes of two sizes: 16 by 150 mm. (20 ml.), and 13 by 100 mm. (8 ml.).

*Reagents.*—(1) Standard histamine, 40 μg histamine base per ml. in 0.01N HCl (66.3 μg histamine dihydrochloride, or 110 μg histamine diphosphate per ml.) stored frozen. (2) Trichloroacetic acid, 10 per cent, stored in the refrigerator. (3) Alkaline phosphate buffer (pH ≅ 11) composed of 150 ml. 4M $K_2HPO_4$, 20 Gm. KBr, 40 ml. 5M NaOH. (4) DNFB, 2 per cent in ethanol. DNFB* prepared in this laboratory was used in the work reported here. The sample tested was only about 50 per cent pure, but gave the same results when used in double the specified quantities. (5) Methyl-n-hexyl ketone, practical grade.† (6) Hydrochloric acid, 2N.

*Procedure.*—(1) Incubate 5 ml. of serum and 0.25 ml. of the standard histamine solution in a 20 ml. test tube for 60 minutes at 56° C.‡ (2) Stop the reaction with 5 ml. 10 per cent trichloroacetic acid. Mix immediately. Centrifuge after standing 30 minutes. (3) Transfer 5 ml. of the supernate to another 20 ml. tube containing 3 ml. of the alkaline phosphate buffer. (4) Add 0.3 ml. of the 2 per cent DNFB; mix each tube immediately after addition of the reagent, and heat 30 minutes in a water bath at 56° C. (5) Cool, add 5 ml. methyl-n-hexyl ketone, shake vigorously (closing tube with thumb), and centrifuge briefly. (6) Transfer 4 ml. of the ketone (upper) layer to an 8 ml. tube containing 1 ml. 2N HCl, shake vigorously (closing tube with thumb), and centrifuge briefly. (7) Remove ketone layer by aspiration or transfer acid (lower) layer to another 8 ml. tube and compare with a standard which is prepared like the test sample except that the standard histamine is added *after* the trichloroacetic acid and before centrifuging.

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*The commercial product is available from the Republic Laboratory, 7 West Madison St., Chicago, Ill.

†Eastman Kodak Company, Rochester, N. Y., or Matheson Co., Joliet, Ill.

‡The amount of serum required may be reduced if desired by using 1 ml. serum plus 4 ml. phosphate buffer pH 6.8 (see Quantitative Test) with a five times longer incubation.

If the yellow color of the acid layer of a test sample is noticeably paler than that from the standard, the woman from whom the sample was taken is pregnant. If there is no color loss, or the color loss is in doubt, the test may be repeated with an incubation time of 4 hours. With samples from pregnancies of 85 or more days' duration, the color loss will always be discernible with the longer incubation when the tubes are viewed side by side.

The time needed to run a single sample including 60 minutes' incubation followed by color development is about three hours. To run 15 samples with this incubation time, four hours would be sufficient. Unless the difference between these times and the 6 hours or so needed with the longer incubation time is critical, use of the longer incubation time in the first run is worth while as it eliminates results in the doubtful range.

## Quantitative Test

*Apparatus.*—A Beckman spectrophotometer is the only special piece of equipment needed. The cells used should have a 10 mm. light path with a 5 mm. inner width.*

*Reagents.*—In addition to the standard and reagents used in the qualitative method, a weak phosphate buffer of the following composition (pH $\cong$ 6.8) is used: 100 ml. 0.02M $KH_2PO_4$ and 100 ml. 0.02M $Na_2HPO_4$.

*Procedure.*—Serum (or plasma) is used diluted or undiluted depending upon its activity and the time desired for incubation (5 minutes to 24 hours). Dilution slows the rate of histamine destruction. A dilution of 1:216 suffices for the longest incubation of the most active serum. For sera obtained after 120 days' gestation and incubated overnight at 38° C., dilutions of 1:36 and 1:216 will cover the range of activity. If the activity of a sample is completely unknown, incubation for at least 16 hours at 38° C. with the use of all dilutions and undiluted serum is recommended.

To dilute: Set up three 20 ml. test tubes with 10 ml. of the weak phosphate buffer in each, and add 2 ml. serum to the first. Mix and transfer 2 ml. from the first tube to the second; again mix and transfer 2 ml. from the second to the third, and mix. These tubes now contain 1:6, 1:36, and 1:216 dilutions of the serum.

(1) Select dilutions desired, and place 2 ml. from this tube into each of four 8 ml. test tubes. Two of these tubes are used for measuring the enzyme activity, while the other two serve as serum standards. To two of these four samples of serum (or dilution) add 0.1 ml. of the standard histamine solution. Incubate all samples (with or without histamine) 5 minutes to 24 hours at either 38° C. or 56° C. At 56° C. the rate of histamine destruction is twice that at 38° C. (2) Stop the reaction with 2 ml. of 10 per cent trichloroacetic acid and mix immediately. To the samples without histamine now add 0.1 ml. standard histamine and mix again. These samples are the serum standards. Centrifuge all samples after standing 30 minutes. (3) Transfer 2 ml. of the supernate to a 20 ml. test tube containing 1 ml. of the alkaline phosphate buffer. (4) Add 0.1 ml. 2 per cent DNFB; mix each tube immediately after the addition of this reagent. Heat 30 minutes in a water bath at 56° C. (5) Cool, and add 5 ml. methyl-n-hexyl ketone, shake vigorously against thumb, and centrifuge. (6) Transfer a 4 ml. aliquot of the ketone to another 8 ml. tube containing 1 ml. 2N HCl; shake vigorously, and centrifuge. (7) Read the optical density (O.D.) of the acid layer at 360 m$\mu$ in the Beckman spectrophotometer. Subtract the average sample reading for each dilution from the corresponding serum standard to obtain "serum net O.D."†

*These are available from the Pyrocell Mfg. Co., 207-211 East 84th St., New York, 28, N. Y.

†The serum standard O.D. is about 0.050 greater than the water standard with undiluted serum. This difference becomes progressively smaller with greater serum dilution.

Each time color is developed water blanks and water standards are prepared. Use water instead of serum, add 0.1 ml. standard histamine to the standards and none to the blanks. Subtract blank reading from the water standard. The difference equals "std. net O.D."

*Micro Adaptation of Quantitative Test.*—

When the necessary equipment is available, this is no more difficult nor time consuming than the regular quantitative method. As little as 0.5 ml. of serum will permit incubation of both undiluted and diluted samples: 0.4 ml. being used for duplicate determinations on undiluted serum and 0.1 ml. for preparing the serum dilutions.

*Apparatus.*—(1) Lang-Levy constriction pipettes* (Levy; Bessey, Lowry, and Brock). (2) 1 ml. test tubes (7 by 70 mm.).† (3) Beckman spectrophotometer equipped with microcuvettes (Lowry and Bessey). The cuvettes‡ should be 1 mm. in inner width with a light path of 1 cm. (4) Buzzer. This provides mechanical mixing by rotation of a slightly bent rod at 2,000 r.p.m. or more. The tubes are held tightly against the rod to provide mixing.

*Reagents.*—The same as for the regular quantitative method.

*Procedure.*—The quantities of material required are less; throughout the procedure constriction pipettes and 1 ml. test tubes are used, and solutions are mixed with a buzzer. Otherwise the procedure is the same as in the regular quantitative method. The dilution tubes are set up with 500 c.mm. of the weak phosphate buffer and 100 c.mm. of serum in the first tube; 100 c.mm. of the dilution is transferred to 500 c.mm. of the weak phosphate buffer in the second, and so on as in the regular quantitative method. The quantities used per tube are the following: 100 c.mm. of serum or dilution; 5 c.mm. standard histamine solution; 100 c.mm. 10 per cent trichloroacetic acid; 100 c.mm. aliquot of the trichloroacetic acid supernate; 50 c.mm. alkaline phosphate buffer; 5 c.mm. of 2 per cent DNFB; 450 c.mm. methyl-n-hexyl ketone; and 50 c.mm. 2N HCl. The corresponding quantities are used in making the blanks and standards.

The quantitative method permits analysis of 10 to 15 samples of blood including necessary dilutions in one day's work. With overnight incubation results from this number of samples can be obtained in about 24 hours. The time of preparation of incubation is 2 to 3 hours, and the time needed the next day to develop color and to read the optical density is about 6 hours.

*Calculations.*—The rate of destruction of histamine at the concentration specified is limited only by the amount of histamine present. Therefore the reaction is of the first order, i.e., the reaction does not proceed at a constant rate, but follows a "die-away" curve similar to the course of radium disintegration. In a certain period of time half the histamine is destroyed, in a succeeding equal period half the remainder is destroyed, etc. The activity may therefore be expressed in terms of the length of time needed to destroy half the added histamine, this "half-life" being inversely proportional to the activity.

The basic formula for calculation of the half-life ($t_{0.5}$) is:

$$t_{0.5} = \frac{1}{\text{dilution}} \times \frac{0.301\ t}{\log \frac{\text{initial concentration}}{\text{final concentration}}}$$

where t = time of incubation in minutes; dilution = 1, 6, 36, or 216, as the case may be; and

$$\log \frac{\text{initial concentration}}{\text{final concentration}} = \log \frac{\text{std. net O.D.}}{\text{std. net O.D. - serum net O.D.}}$$

*These may be made or may be bought from the Arthur H. Thomas Co., Philadelphia, or the Micro Chemical Specialties Co., Berkeley, Calif.

†Available from the Arthur H. Thomas Co.

‡Available from Pyrocell Mfg. Co., 207 E. 84th St., New York 28, N. Y.

All half-life values given in this paper were determined by the microquantitative method at 38° C. To convert to 38° C. the half-life values obtained at 56° C., the half-life values should be doubled.

For example:

A pregnancy sample incubated 18.0 hours at 38° C. at a 1:36 dilution gave the following optical density readings: water standard 0.150, water blank 0.025, serum standard 0.160, serum test sample 0.110.

$$t_{0.5} = \frac{1}{36} \times \frac{0.301 \times 18 \times 60}{\log \frac{0.150 - 0.025}{(0.150 - 0.025) - (0.160 - 0.110)}}$$

$$t_{0.5} = \frac{9.03}{\log \frac{0.125}{0.075}} = \frac{9.03}{0.222} = 40.7 \text{ minutes}$$

## Comment

*Effects of Experimental Conditions on Histaminolytic Activity.*—Although as a matter of convenience serum is recommended for use in the pregnancy test, and was used in obtaining most of the results recorded in this paper, the histaminolytic activity may also be measured in plasma. Citrate, oxalate, or heparin is a satisfactory anticoagulant.

TABLE I. STABILITY OF HISTAMINASE IN THE BLOOD AT ROOM TEMPERATURE

Aliquots of a single sample of pregnancy blood were left at room temperature for the times indicated and then stored frozen until analyzed.

| HOURS AT ROOM TEMPERATURE | 1 | 2 | 6 | 24 | 48 |
|---|---|---|---|---|---|
| $t_{0.5}$ (minutes) | 7.0 | 5.7 | 6.2 | 7.6 | 6.1 |

Serum stored at −10° C. undergoes no significant loss of activity in about a year (Table IV); at room temperature there is no loss of activity for at least 48 hours (Table I); and even at 56° C. the activity shows no decrease in a number of hours, although according to Ahlmark the rate of the reaction decreases rapidly as the temperature is increased above 58° C. A slight change in temperature markedly affects the rate of the reaction in the range where the enzyme is stable and active, as shown by the doubling of the rate of the reaction between 38° C. and 56° C. Careful control of the incubation temperature is therefore necessary for results comparable from experiment to experiment. Hemolysis does not seem to interfere with enzyme activity.

The initial histamine concentration suggested here, 2 μg. per milliliter (approximately that used by Ahlmark), seems to be about the optimum, since the maximum velocity of histamine destruction is reached at concentrations very little above this. As the histamine concentration is increased, the *relative* amount destroyed becomes less, and therefore is less accurately determined. As the concentration of substrate is further increased actual inhibition was observed; this is in agreement with the findings of Zeller and Birkhäuser (1940). These workers used a colorimetric method based on the oxidation of indigo sulfonate for the estimation of histamine. In contrast Kapeller-Adler (1951), using a modification of the indigo sulfonate method involving incubation in an atmosphere of oxygen instead of air, found no inhibition of the reaction at concentrations up to 150 μg. of histamine base per milliliter. An attempt to confirm Kapeller-Adler's observation with incubation in an atmosphere of oxygen using the DNFB method was unsuccessful. The discrepancy remains unexplained.

*Method of Expressing Histaminolytic Activity.*—Histaminolytic activity has been expressed by earlier authors in terms of the amount of histamine destroyed in a given time under given conditions. Because the rate of destruction varies directly with the concentration of histamine below the optimum concentration (initial concentration of these experiments), and inversely with the concentration of histamine above the optimum (see preceding paragraph), such expressions for activity are comparable only when they are derived from experiments in which both the initial and final histamine concentrations are the same. These conditions are rarely fulfilled in work from different laboratories. On the other hand the half-life for a given amount of activity is a constant for all quantities of histamine below the optimum concentration (2 μg. per milliliter), and is independent of the time of incubation.

Accuracy is greatest when 20 to 80 per cent of the histamine is destroyed. Active samples can always be diluted enough to measure both the histamine destruction and the time interval accurately. Very inactive samples do not destroy enough histamine after an overnight incubation to measure the destruction accurately; an increase of incubation over 24 hours does not increase accuracy. Therefore samples having a half-life value of 10,000 minutes or more are regarded as having an infinite half-life.

*Reproducibility of Results.*—The reproducibility of half-life values obtained is demonstrated in Table II for different durations of incubation; in Table III for different dilutions of serum run on the same day; and in Table IV for determinations on different days after varying times of storage of the serum. The average difference in half-life value in Table II is 5 per cent; in Table III, 11 per cent; and even in Table IV, which involves maximum discrepancy in conditions of color development, it is only 29 per cent. Compared to the average of five hundred fold decrease in half-life during pregnancy, this is an insignificant variation.

TABLE II. VALUES OF $t_{0.5}$ OF ONE SAMPLE CALCULATED FROM DIFFERENT TIMES OF INCUBATION

Pregnancy serum undiluted

| TIME OF INCUBATION (MINUTES) | HISTAMINE DESTROYED (μG./ML.) | $t_{0.5}$ (MINUTES) | DEVIATION OF $t_{0.5}$ FROM AVERAGE (PER CENT) |
|---|---|---|---|
| 5 | 0.17 | 35 | 0 |
| 11 | 0.35 | 35 | 0 |
| 20 | 0.64 | 32 | 9 |
| 30 | 0.76 | 39 | 10 |
| | Average | 35 | 5 |

## Histaminolytic Activity in Pregnancy Sera

Histaminolytic activity was determined in 151 samples of serum from 44 pregnant women, one sample from one woman suspected of pregnancy but who gave a negative frog test and a negative test by this method, one sample of pooled plasma from 3 men, and 4 weekly samples of serum from each of two nonpregnant healthy women of childbearing age. None of the patients suffered from toxemia of pregnancy. One patient bore twins, one aborted at three months, and another had a premature labor at six months. Ten of the patients stopped coming to the clinic during their pregnancy. The rest of the patients gave birth to full-term healthy babies and suffered no complications during the puerperium.

TABLE III. COMPARISON OF $t_{0.5}$ CALCULATED FROM TWO DILUTIONS OF VARIOUS PREGNANCY SERA

Values are for $t_{0.5}$ in minutes

| SERUM NO. | SERUM DILUTIONS | | | | DIFFERENCE BETWEEN $t_{0.5}$ VALUES (PER CENT) |
|---|---|---|---|---|---|
| | 1:1 | 1:6 | 1:36 | 1:216 | |
| 1 | 760 | 780 | | | 3 |
| 2 | 580 | 510 | | | 14 |
| 3 | | 76 | 60 | | 21 |
| 4 | | 76 | 93 | | 18 |
| 5 | | | 25 | 26 | 4 |
| 6 | | | 21 | 22 | 4 |
| 7 | | | 21 | 18 | 14 |
| 8 | | | 16 | 14 | 13 |
| 9 | | | 16 | 17 | 6 |
| 10 | | | 12 | 10 | 17 |
| | | | | Average | 11 |

TABLE IV. COMPARISON OF $t_{0.5}$ OF VARIOUS SAMPLES DETERMINED ON SEPARATE DAYS

Pregnancy sera stored frozen between determinations

| SERUM NO. | INTERVAL BETWEEN DETERMINATIONS (DAYS) | FIRST DETERMINATION $t_{0.5}$ (MINUTES) | SECOND DETERMINATION $t_{0.5}$ (MINUTES) | DIFFERENCE IN VALUES (PER CENT) |
|---|---|---|---|---|
| 1 | 304 | 620 | 540 | 13 |
| 2 | 35 | 43 | 25 | 42 |
| 3 | 2 | 43 | 33 | 23 |
| 4 | 4 | 39 | 25 | 36 |
| 5 | 1 | 18 | 22 | 18 |
| 6 | 4 | 17 | 40 | 57 |
| 7 | 4 | 16 | 12 | 25 |
| 8 | 4 | 12 | 15 | 20 |
| 9 | 25 | 10 | 7.3 | 27 |
| | | | Average | 29 |

Nonpregnancy sera gave half-life values ranging from 3,590 minutes to over 10,000 minutes. The values did not seem to be influenced by the phase of the menstrual cycle in the two women tested weekly.

The half-life values found in pregnancy sera have been of necessity plotted on a logarithmic scale because of the tremendous range they cover (Fig. 1). Pregnancy samples taken about the sixtieth day after the last menstrual period all showed greater activity than the most active nonpregnancy sample. One sample from the forty-ninth day also showed greatly increased activity, whereas four other samples before the fifty-first day fell within the nonpregnancy range. As pregnancy progressed, the activity increased very rapidly to a maximum (median half-life, 9 minutes) maintained from about 165 days to 230 days; after this it decreased slightly. The median activity of the last half of pregnancy was over 200 times the minimum normal activity. A twenty-five fold variation of activity was observed at any given duration of pregnancy. Successive values for any one patient followed a relatively consistent level (Fig. 2), although those whose serum showed a maximum activity early seemed to lose more of this activity at term than those whose serum was relatively less active at an early stage.

Samples taken 3 to 4 weeks before abortion in one case and premature delivery in another both gave values within the limits expected for the duration of their pregnancies. The same is true of samples from a woman who had twins. No samples were obtained late in the twin pregnancy.

The levels and course of development of activity during pregnancy reported here are essentially the same as those found by others. Anrep, Barsoum, and Ibrahim (1947) found that activity increased steadily to the end of pregnancy. Kapeller-Adler (1951) found a sharp drop in the activity after the sixth month (cases of twin pregnancies being the only exceptions), instead of a fairly constant level for the next two and one-half months as here. Ahlmark found a slight decrease at the end of the seventh month with a rise again to the earlier maximum just before term.

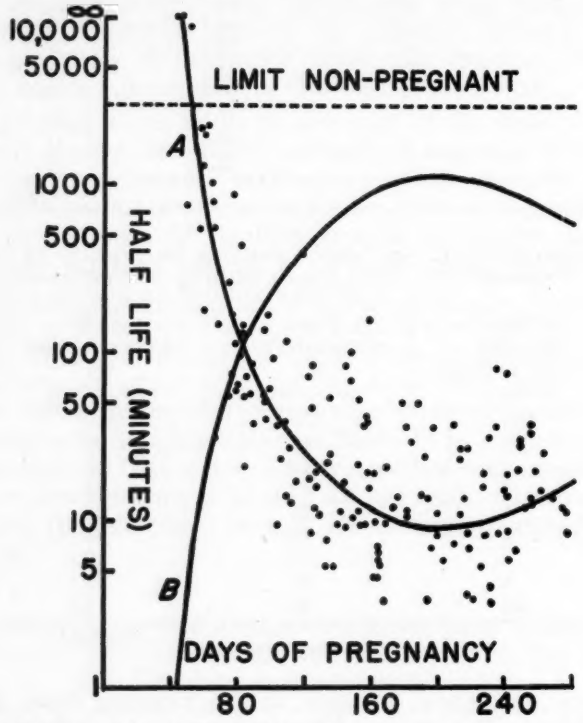


Fig. 1.—Histaminase activity during the course of pregnancy.

Values were obtained from 151 sera from 44 pregnant women. "Half life (minutes)" is number of minutes necessary to destroy half the added histamine (0.9 μg. histamine base per milliliter serum). See text. The dotted line labelled "limit nonpregnant" represents the shortest half-life obtained from a nonpregnant person. *A* is the curve representing the median of these points; *B* is reciprocal of *A* representing the increase of histaminolytic activity during pregnancy.

In a group of about 45 pregnancies Ahlmark found only a fivefold range of histaminolytic activity at any given period during the last half of pregnancy, his maximum activity being roughly two-thirds, and his minimum, three times as great as the samples in the present series. He also found that successive values for any one patient followed a relatively consistent level. Kapeller-Adler (1951) found a range of only about 25 per cent from the average value at any given period of pregnancy excluding toxemias and multiple pregnancies. It is difficult to explain why such different ranges should be found in Ahlmark's, Kapeller-Adler's, and this series.

The probable source of this histaminolytic activity is the maternal side of the placenta and adjacent decidua. Ahlmark found great activity in extracts of minced placenta. Swanberg found that much greater activity per unit weight could be obtained from scrapings of the maternal side of the placenta and of removed decidual septa than from the rest of the placenta. Each of these investigators found the activity of the maternal plasma in cases of

hydatidiform mole corresponded to the expected activity from a normal placenta of the same age; Swanberg, however, found that the mole itself contained no activity.

The rise in the histaminolytic activity in the plasma occurs while both the placenta and decidua are increasing rapidly in weight. It lags about two weeks behind the appearance of histologically mature secondary villi. The marked decrease in activity at the end of pregnancy in some cases may be related to the senility of the placenta and decidua, as it is known that some placentas show more evidence of senility at term than others. No correlation could be found between the activity and the duration of pregnancy, the size, or the sex of the baby in either this series or Swanberg's.

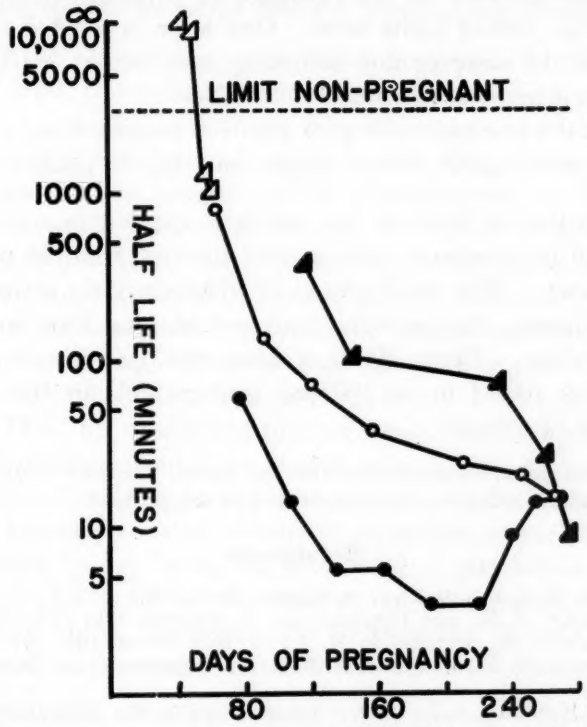


Fig. 2.—Individual changes in serum histaminase during pregnancy.

Successive values from 4 healthy, pregnant women are plotted, and individual curves drawn. "Half life (minutes)" is number of minutes necessary to destroy half the added histamine (0.9 μg. histamine base per milliliter serum). See text. The dotted line labelled "limit nonpregnant" represents the shortest half-life obtained from a nonpregnant person.

The colorimetric test of histaminolytic activity in its quantitative form proved completely reliable from 60 days after the last menstrual period until term, that is, there were no false negatives in 44 pregnancies. (Not enough samples were obtained before 60 days to state with certainty which is the earliest day when a rise in activity can ever be found, and which is the latest day that a pregnant woman can give a value within nonpregnancy limits.) There were likewise no false positives, but the number of cases is small. The guinea pig assay of histaminolytic activity proved similarly reliable in Ahlmark's hands. He found no false positives in 36 tests on men and nonpregnant women, and no false negatives in about 45 pregnancies after about 60 days. Increased activity was found in 3 cases of hydatidiform mole; one might anticipate increased activity in chorionepithelioma. In contrast to the pregnancy tests based on histaminolytic activity, those based on chorionic gonadotropin become

less accurate after 4 months of pregnancy, and when term is approached may sometimes give negative results. Available data suggest that at the beginning of pregnancy the increase in histaminolytic activity lags behind the increase in chorionic gonadotropin by about two weeks.

## Summary

1. A new colorimetric test for pregnancy based on the histaminolytic activity of pregnancy plasma is described.

2. The test in its simple and rapid qualitative form will give a yes or no answer to the question of the presence of pregnancy from 85 days after the last menstrual period until term. One hour is needed to determine the activity of about 15 samples not including incubation; including incubation a period of about 4 hours is necessary.

3. The quantitative test will give positive results from 60 days after the last menstrual period until term. About one day is needed to determine 10 to 15 samples.

4. The quantitative form of the test was applied to over 160 samples of serum, 11 from 6 nonpregnant persons and the rest from 44 women in various stages of pregnancy. The development of histaminolytic activity was followed throughout pregnancy; the activity increases at least two hundred fold over nonpregnancy values. From 60 days after the last menstrual period until term the test was found to be 100 per cent reliable in this series (no false negatives or false positives).

I wish to express my appreciation to Dr. Helen Tredway Graham, Dr. Oliver H. Lowry, and Dr. Willard Allen for their interest and suggestions.

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# THE DURATION OF THE SECOND STAGE OF LABOR*

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THE origin of the second stage rule which in essence limits the duration of this phase of labor to two hours cannot really be assigned to any one individual. It grew out of a protest against the restrictive ideas of such men as William Hunter, Osborne, and Denman, whose authority, during the first half of the nineteenth century, was so revered and so absolute that the use of forceps to shorten labor as a whole, and in particular the second stage, was practically banished from good practice. The death of the Princess Charlotte of Wales in 1817, recently so superbly told by Sir Eardley Holland,[1] gives a graphic portrayal of the blind faith in nature, and the supine inactivity of the obstetricians of that day. Although Denman[2] was part and parcel of this retrograde phase of obstetrical evolution, he was the first to put a time limit on the second stage of labor. Thus, he established the law which bears his name, that the use of forceps is not indicated until the second stage of labor has lasted six hours and all other means of delivery have been tried. It is interesting that Merriman,[3] who was one of Denman's ardent disciples, suggested as early as 1810 that the six-hour rule might be too stringent, and cited a case where he had effected delivery of an infant after a second stage of only two hours without detriment to either mother or child. However, the influence of the old masters was too strong, and in his book, published in 1820, Merriman[4] writes as follows:

"The forceps shall never be applied until the ear of the child has been within reach of the operator's finger for at least six hours." Revolt against these extreme rules was probably inaugurated by the German obstetricians who were not so directly influenced by English authorities. In particular Siebold,[5] although he mentions no time limit for the second stage, indicates that the life of the child when endangered by prolongation of the second stage furnishes an indication for forceps delivery. In 1829, the older Beatty,[6] in a paper before the College of Physicians of Dublin, pointed out that in his own practice he had employed the forceps 105 times in 5,616 deliveries and stated quite clearly the indications for the use of the instrument and the great benefit which could be derived from it in appropriate cases. Mr. Philip Harper[7] published a table from the statistics of the Rotunda Hospital achieved by the various masters prior to 1859 (Table I). It indicates a definite diminution in maternal and infant deaths derived from the more frequent use of the forceps. Harper himself set no time limit upon the second stage, but felt that the forceps were better used too early rather than too late. He was certainly of the opinion that a six-hour delay was too long. Sir James Y. Simpson[8] also made use of statistics to show that, for labor as a whole, danger was proportionate to delay.

*Read before the Brooklyn Gynecological Society, Feb. 20, 1952.

TABLE I. DIMINUTION OF FETAL AND MATERNAL MORTALITY WITH INCREASING USE OF FORCEPS AND SHORTENING OF LABOR*

| PHYSICIANS | FORCEPS CASES | FETAL DEATHS | MATERNAL DEATHS | DURATION LABOR |
|---|---|---|---|---|
| Collins | 1 in 694 | 1 in 26 | 1 in 329 | 38 hours |
| Hardy | 1 in 355 | 1 in 20 | 1 in 334 | 35½ hours |
| Johnston | 1 in 60 | 1 in 35 | 1 in 502 | 29½ hours |
| Harper | 1 in 26 | 1 in 47 | 1 in 1,490 | 16 hours |

*Mr. Philip Harper, Transactions Obst. Society of London, 1859.

Hamilton[9, 10, 11] became an ardent advocate of the forceps to shorten the second stage of labor. In a series of papers published from 1853 through 1871, he showed a surprisingly low infant mortality and maternal morbidity, using the forceps in approximately one case in five. In his two series, comprising 800 and 700 deliveries, respectively, there was not a single stillbirth when forceps were employed. In his second paper, published in 1861, appears the first real mention of the two-hour second stage rule. I quote as follows: "Whenever the os has become fully dilated, so that an ear can be felt, I hold that the danger to the child usually becomes imminent if allowed to remain undelivered much more than 2 hours."

In 1877, Dunster*[12] wrote what was probably the first American paper on this subject under the title, "The Use of the Obstetrical Forceps in Abbreviating the Second Stage of Labor." This author gave no rule for the duration of the second stage but was clearly in agreement with Hamilton. The paper is remarkable in that it definitely forecasts the prophylactic use of the obstetric forceps promulgated by Dr. DeLee[13] 42 years later. This paper was followed in the next year by one by Fauntleroy.[14] In both publications, statistics are employed to indicate that the use of forceps to shorten the second stage of labor will save both maternal and infant lives. The two-hour rule seems to have been fairly definitely established in American texts by 1894 (Landis[15]). In the first edition of Williams, published in 1903, it is definitely stated that forceps are usually indicated if the second stage has lasted more than two hours. There still was no universal agreement, however, on the exact time at which the second stage should be terminated (Polak, 1913[16]; DeLee, 1918[17]). The paper by DeLee on the prophylactic forceps read before the American Gynecological Society in 1920, while not immediately accepted, more or less terminated this argument, for the majority of deliveries were then accomplished long before two hours of second stage. In prolonged labors it still was a matter of pretty general practice to terminate labor by forceps if the second stage progressed much beyond two hours. This practice often led to the performance of difficult forceps operations, and the question was raised in the minds of many obstetricians, whether prolongation of the second stage until such a time as an easy forceps delivery might be accomplished would not be of some advantage. The true answer to the question of the effect of the duration of the second stage of labor upon mother and infant could be answered only by a thorough study of a large number of fairly normal deliveries. With this in mind the following investigation was undertaken.

## Material

The period from Jan. 1, 1937, to Dec. 31, 1949, at the Johns Hopkins Hospital, furnished a particularly advantageous time for such a study. From 1936 on, the Department, under the influence of a new chief, had become less rigid in its concepts, and had begun to explore some of the more modern methods of obstetrical care. Certain practices were initiated which should influence the duration of labor, particularly as it concerns the second stage. Among the most obvious of these was the employment of the prophylactic forceps,

*Reference kindly furnished by Dr. Claude Heaton, New York.

the administration of pain relief to ward patients, and the growth and understanding of the place of accurate x-ray pelvimetry in obstetrics. In particular, the prophylactic forceps tended to shorten the second stage. Whereas formerly the rule was to wait two hours, and only two hours, before accomplishing forceps delivery, many patients were now safely delivered prior to this time. Furthermore, with the more liberal indications for forceps, and the realization that the patients were not suffering, it became more and more the practice to disregard the two-hour rule and to allow the second stage to continue until such a time as an easy low forceps delivery was practical. There was thus accumulated a large mass of material with a good spread of second-stage durations, particularly well fitted for just such a study as this. It seemed that from this material the question of whether prolongation of the second stage was really harmful to the mother or to her infant, and, if so, at what point might be answered.

While it is manifestly impossible to study the second stage of labor "in pure culture," eliminating all extraneous factors, such as the size of the pelvis, length of the first stage, type of delivery, and so forth, certain modifications in the population to be studied will tend to eliminate many of them. Thus, patients with the following complications have been removed from the group: premature deliveries, abnormal presentations, multiple pregnancies, hypertensive patients of all types, patients with fetal heart not heard on admission, cesarean section, placenta previa, premature separation of placenta, fetal abnormalities, patients with unmeasured pelves, and patients with second stage of unknown duration.

There remained 13,377 deliveries with a fetal loss rate of 0.48 per cent, in which it could be assumed that the effect of prolongation of the second stage might be truly assessed. Table II shows the population to be studied divided according to race, parity, type of delivery, and type of pelvis.

TABLE II. ANALYSIS OF 13,377 DELIVERIES EMPLOYED IN THE SECOND STAGE STUDY, JOHNS HOPKINS HOSPITAL, JAN. 1, 1937, TO DEC. 31, 1949

| | PRIMIPARAS | | MULTIPARAS | |
|---|---|---|---|---|
| | DELIVERIES | PERCENTAGE | DELIVERIES | PERCENTAGE |
| Spontaneous | 2,511 | 39.5 | 5,633 | 80.3 |
| Forceps | 3,849 | 60.5 | 1,384 | 19.7 |
| Normal pelvis | 4,725 | 74.3 | 5,481 | 78.1 |
| Contracted pelvis | 1,635 | 25.7 | 1,536 | 21.9 |
| White | 3,511 | 55.2 | 4,209 | 60.0 |
| Negro | 2,849 | 44.8 | 2,808 | 40.0 |

Fig. 1 shows the distribution of these cases according to minutes of second stage. It is interesting to note that 92 per cent of these patients have been delivered within two hours, while nearly 77 per cent have been delivered within one hour. Nevertheless, there remained 1,034 patients in whom delivery was not accomplished until after two hours of the second stage. This furnishes a good sample for a study of this type. Figs. 2 and 3 show the effect of race and parity and of pelvis and parity upon the duration of the second stage. In Fig. 4 the influence of the position of the infant upon the duration of the second stage is demonstrated. In all of these charts the median duration of the second stage has been used. In instances such as the duration of the second stage of labor, where the majority of cases fall into the fairly short category, there is a skew distribution. Such a distribution is more accurately summarized by the median rather than the mean. This was clearly brought out in the paper by Busby[18] on the duration of labor. It would appear that race per se has very little effect on the duration of the second stage of labor. Negro multiparas have a slightly longer second stage while white primiparas take slightly longer to terminate labor. However, these differences are not significant. The median

duration of the second stage of labor is slightly under 20 minutes for multiparas, and slightly under 50 minutes for primiparas. While these figures are in general agreement with the accepted teachings as to the duration of the second stage of labor in multiparas, they are somewhat shorter than those commonly taught for primiparas. The reason for this discrepancy is the use of the median rather than the mean. In multiparas the presence of pelvic contraction would appear to have little effect upon the duration of the second stage. However, in primiparas it causes some prolongation. It must be remembered that in this series severe degrees of pelvic contraction have been eliminated through the use of x-ray pelvimetry.

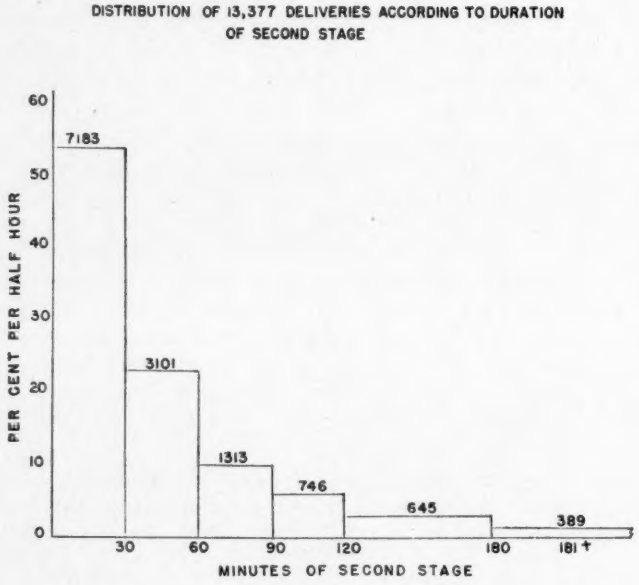


Fig. 1.

Fig. 4 shows the correlation between fetal position and minutes of second stage. It becomes quite obvious that the posterior positions and in particular those that are persistently posterior have a rather pronounced effect upon the prolongation of the second stage of labor.

In order to assess truly the effects of the duration of the second stage on the outcome of labor, one must also know the role played by the duration of the first stage. In addition, it becomes important to determine whether prolongation of the first stage is associated with a similar prolongation of the second stage, and if so, to what degree. Table III and Fig. 5 show this relationship. Prolongation of the first stage can be seen to be definitely correlated with a significant and progressive increase in the duration of the second stage up to 20 hours. The probability of this association occurring by chance is less than 2 per cent.* Beyond 20 hours, however, prolongation of the first stage has little or on significant effect upon the duration of the second stage of labor. This being the case, in studying the effect of the duration of the second stage upon such complications as intrapartum fever, postpartum hemorrhage, and postpartum febrility, and, finally, infant mortality, it seemed reasonable to exclude those instances where the second stage lasted 20 hours or more. This

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* 0-4 and 5-9 hours Standard error 6.43P < .0001
5-9 and 10-14 Standard error 8.43P < .0001
10-14 and 15-19 Standard error 2.31P = .020
15-19 and 20-24 Standard error 0.83P = .406
20-24 and 25-29 Standard error 0.64P = .522
25-29 and 30 + Standard error 0.15P = .880

should, so far as is obtainable from these data, give a second-stage effect in relatively "pure culture." The converse should also be true, namely, the removal of cases with second stages of two hours or more should give the first-stage effect unhindered by the prolongation of the second stage.

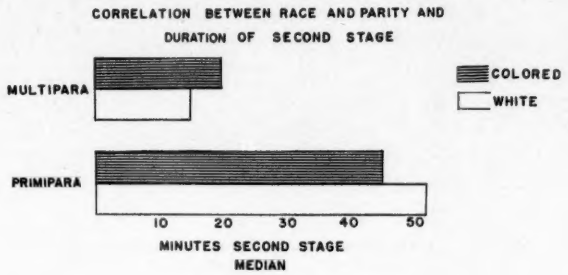


Fig. 2.

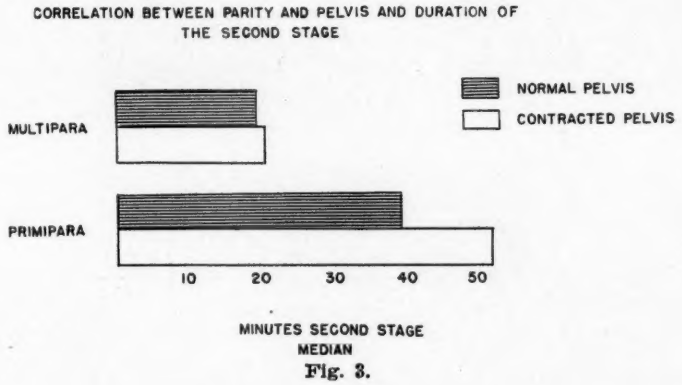


Fig. 3.

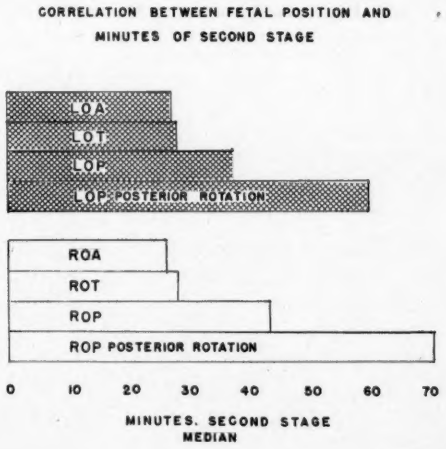


Fig. 4.

Such data are presented in Tables IV, V, VI, and VII, and graphically in Figs. 6, 7, 8, and 9.

Examination of Fig. 6 indicates that the prolongation of the second stage of labor plays a more important role in the causation of postpartum hemorrhage than does prolongation of the first stage, the incidence rising from 3.8 per cent to 7.3 per cent in first stages of less than 5 hours to first stages of more than 30 hours, while the incidence rises from 3.3 per cent in second stages of less than

TABLE III. CORRELATION BETWEEN HOURS OF FIRST STAGE AND MINUTES OF SECOND STAGE

| HOURS OF FIRST STAGE | TOTAL | 1 0-30 | 2 31-60 | 3 61-90 | 4 91-120 | 5 121-180 | 6 181+ |
|---|---|---|---|---|---|---|---|
| 5 | 3,372 | 2,375 | 612 | 195 | 86 | 70 | 34 |
| 5-9 | 4,813 | 2,689 | 1,117 | 453 | 247 | 198 | 109 |
| 10-14 | 2,533 | 1,118 | 682 | 305 | 182 | 153 | 93 |
| 15-19 | 1,300 | 512 | 348 | 171 | 107 | 99 | 63 |
| 20-24 | 623 | 223 | 179 | 83 | 54 | 51 | 33 |
| 25-29 | 309 | 106 | 81 | 44 | 26 | 35 | 17 |
| 30+ | 422 | 159 | 82 | 61 | 43 | 39 | 38 |
| Unknown | 5 | 1 | 0 | 1 | 1 | 0 | 2 |
| Total | 13,377 | 7,183 | 3,101 | 1,313 | 746 | 645 | 389 |

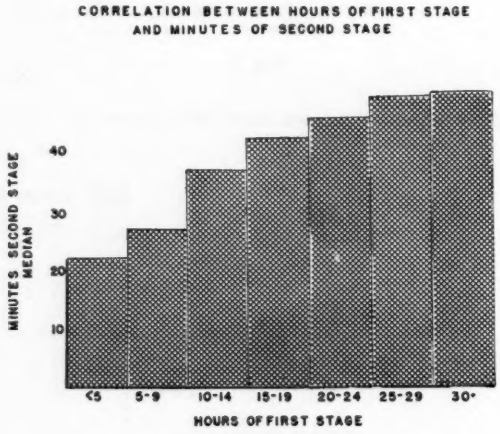


Fig. 5.

TABLE IV. POSTPARTUM HEMORRHAGE

EFFECT OF DURATION OF SECOND STAGE
FIRST STAGE OF 20 HOURS AND MORE ELIMINATED

| MINUTES SECOND STAGE | NO. OF CASES | CASES POSTPARTUM HEMORRHAGE | PERCENTAGE | FIRST STAGE 20 HOURS AND OVER ELIMINATED | | |
|---|---|---|---|---|---|---|
| | | | | NO. OF CASES | POSTPARTUM HEMORRHAGE | PERCENTAGE |
| 0-30 | 7,183 | 238 | 3.31 | 6,695 | 214 | 3.2 |
| 31-60 | 3,101 | 155 | 4.99 | 2,759 | 141 | 5.1 |
| 61-90 | 1,313 | 66 | 5.02 | 1,125 | 52 | 4.6 |
| 91-120 | 746 | 30 | 4.02 | 623 | 19 | 3.0 |
| 121-180 | 645 | 37 | 5.73 | 520 | 31 | 6.0 |
| 181+ | 389 | 40 | 10.28 | 321 | 31 | 9.7 |

EFFECT OF DURATION OF FIRST STAGE
SECOND STAGE OF 121 MINUTES AND OVER ELIMINATED

| HOURS FIRST STAGE | NO. OF CASES | CASES POSTPARTUM HEMORRHAGE | PERCENTAGE | SECOND STAGE 121 MINUTES AND OVER ELIMINATED | | |
|---|---|---|---|---|---|---|
| | | | | NO. OF CASES | POSTPARTUM HEMORRHAGE | PERCENTAGE |
| <5 | 3,372 | 131 | 3.88 | 3,258 | 120 | 3.7 |
| 5-9 | 4,813 | 184 | 3.82 | 4,506 | 163 | 3.6 |
| 10-14 | 2,533 | 109 | 4.30 | 2,287 | 90 | 3.9 |
| 15-19 | 1,300 | 62 | 4.77 | 1,138 | 50 | 4.4 |
| 20-24 | 623 | 33 | 5.30 | 548 | 28 | 5.1 |
| 25-29 | 309 | 15 | 4.85 | 257 | 12 | 4.7 |
| 30+ | 422 | 31 | 7.35 | 365 | 25 | 6.8 |

30 minutes to 10.2 per cent in second stages of over 3 hours. However, in each category removal of the patients with prolonged second stage and the removal of those with prolonged first stage, respectively, still yields similar curves. It

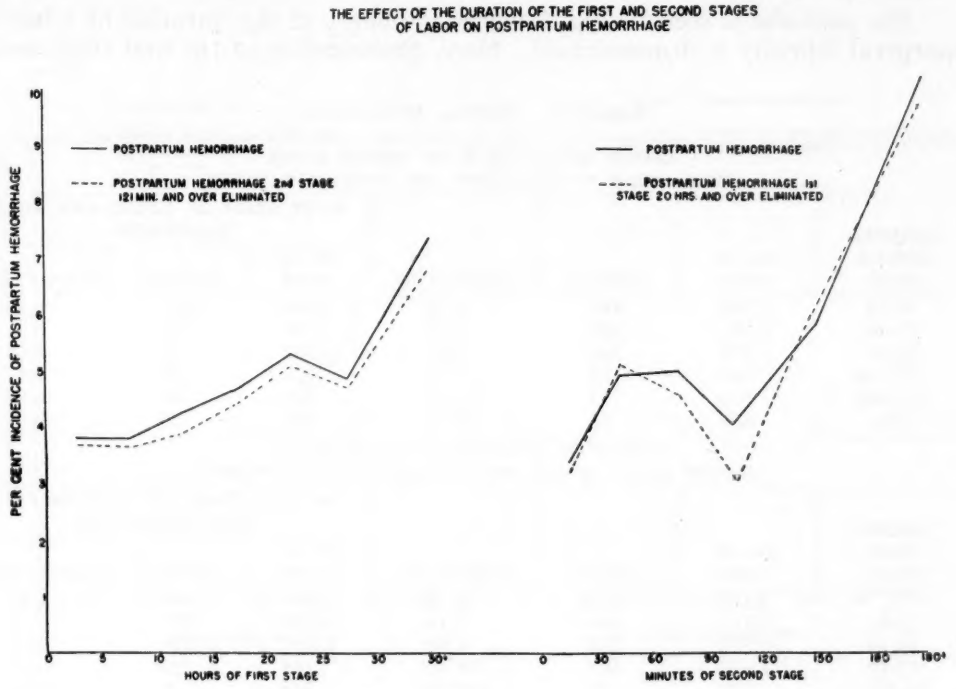
THE EFFECT OF THE DURATION OF THE FIRST AND SECOND STAGES OF LABOR ON POSTPARTUM HEMORRHAGE
PER CENT INCIDENCE OF POSTPARTUM HEMORRHAGE
POSTPARTUM HEMORRHAGE
POSTPARTUM HEMORRHAGE 2nd STAGE 121 MIN. AND OVER ELIMINATED
HOURS OF FIRST STAGE
POSTPARTUM HEMORRHAGE
POSTPARTUM HEMORRHAGE 1st STAGE 20 HRS. AND OVER ELIMINATED
MINUTES OF SECOND STAGE

Fig. 6.

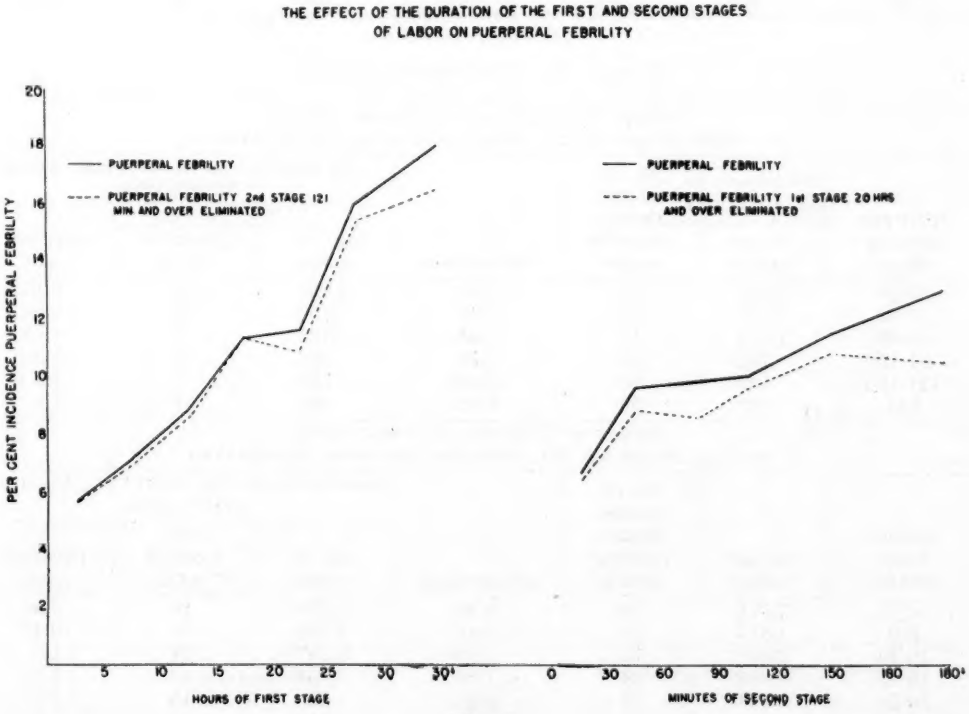
THE EFFECT OF THE DURATION OF THE FIRST AND SECOND STAGES OF LABOR ON PUERPERAL FEBRILITY
PER CENT INCIDENCE PUERPERAL FEBRILITY
PUERPERAL FEBRILITY
PUERPERAL FEBRILITY 2nd STAGE 121 MIN. AND OVER ELIMINATED
HOURS OF FIRST STAGE
PUERPERAL FEBRILITY
PUERPERAL FEBRILITY 1st STAGE 20 HRS AND OVER ELIMINATED
MINUTES OF SECOND STAGE

Fig. 7.

can, therefore, be said that both the second and the first stage, in themselves, effect the occurrence of postpartum hemorrhage, the former having perhaps a little more weight.

The converse is seen in Fig. 7 where the effect of the duration of labor on puerperal febrility is demonstrated. Here, prolongation of the first stage seems

TABLE V. FEBRILE PUERPERIUM

| EFFECT OF DURATION OF SECOND STAGE FIRST STAGE OF 20 HOURS AND MORE ELIMINATED | | | | | | |
|---|---|---|---|---|---|---|
| | | | | FIRST STAGE 20 HOURS AND MORE ELIMINATED | | |
| MINUTES SECOND STAGE | NO. OF CASES | FEBRILE | PERCENTAGE | NO. OF CASES | FEBRILE | PERCENTAGE |
| 0-30 | 7,183 | 483 | 6.72 | 6,695 | 426 | 6.4 |
| 31-60 | 3,101 | 298 | 9.61 | 2,759 | 246 | 8.9 |
| 61-90 | 1,313 | 129 | 9.82 | 1,125 | 96 | 8.5 |
| 91-120 | 746 | 75 | 10.05 | 623 | 60 | 9.6 |
| 121-180 | 645 | 74 | 11.47 | 520 | 56 | 10.8 |
| 181+ | 389 | 51 | 13.11 | 321 | 34 | 10.6 |
| EFFECT OF DURATION OF FIRST STAGE SECOND STAGE OF 121 MINUTES AND MORE ELIMINATED | | | | | | |
| | | | | SECOND STAGE 121 MINUTES AND MORE ELIMINATED | | |
| HOURS FIRST STAGE | NO. OF CASES | FEBRILE | PERCENTAGE | NO. OF CASES | FEBRILE | PERCENTAGE |
| 5 | 3,372 | 193 | 5.72 | 3,258 | 183 | 5.6 |
| 5-9 | 4,813 | 346 | 7.18 | 4,506 | 320 | 7.1 |
| 10-14 | 2,533 | 223 | 8.80 | 2,287 | 198 | 8.7 |
| 15-19 | 1,300 | 149 | 11.46 | 1,138 | 129 | 11.4 |
| 20-24 | 623 | 73 | 11.72 | 548 | 60 | 10.9 |
| 25-29 | 309 | 50 | 16.18 | 257 | 40 | 15.6 |
| 30+ | 422 | 76 | 18.01 | 365 | 61 | 16.6 |

TABLE VI. INTRAPARTUM FEVER

| EFFECT OF DURATION OF SECOND STAGE FIRST STAGE OF 20 HOURS AND MORE ELIMINATED | | | | | | |
|---|---|---|---|---|---|---|
| | | | | 20 HOURS AND MORE FIRST STAGE ELIMINATED | | |
| MINUTES SECOND STAGE | NO. OF CASES | NO. OF CASES INTRA-PARTUM FEVER | PERCENTAGE | NO. OF CASES | INTRA-PARTUM FEVER | PERCENT-AGE |
| 0-30 | 7,183 | 52 | 0.72 | 6,695 | 30 | 0.45 |
| 31-60 | 3,101 | 35 | 1.12 | 2,759 | 19 | 0.69 |
| 61-90 | 1,313 | 19 | 1.44 | 1,125 | 9 | 0.80 |
| 91-120 | 746 | 20 | 2.66 | 623 | 11 | 1.8 |
| 121-180 | 645 | 16 | 2.48 | 520 | 7 | 1.3 |
| 181+ | 389 | 26 | 6.65 | 321 | 15 | 1.6 |
| EFFECT OF DURATION OF FIRST STAGE SECOND STAGE OF 121 MINUTES AND MORE ELIMINATED | | | | | | |
| | | | | SECOND STAGE 121 MINUTES AND MORE ELIMINATED | | |
| HOURS FIRST STAGE | NO. OF CASES | NO. OF CASES INTRA-PARTUM FEVER | PERCENTAGE | NO. OF CASES | INTRA-PARTUM FEVER | PERCENT-AGE |
| <5 | 3,372 | 14 | 0.42 | 3,258 | 13 | 0.40 |
| 5-9 | 4,813 | 21 | 0.44 | 4,506 | 19 | 0.42 |
| 10-14 | 2,533 | 32 | 1.26 | 2,287 | 24 | 1.0 |
| 15-19 | 1,300 | 24 | 1.85 | 1,138 | 13 | 1.1 |
| 20-24 | 623 | 22 | 3.53 | 548 | 15 | 2.7 |
| 25-29 | 309 | 13 | 4.21 | 257 | 10 | 3.9 |
| 30+ | 422 | 42 | 9.95 | 365 | 32 | 8.8 |

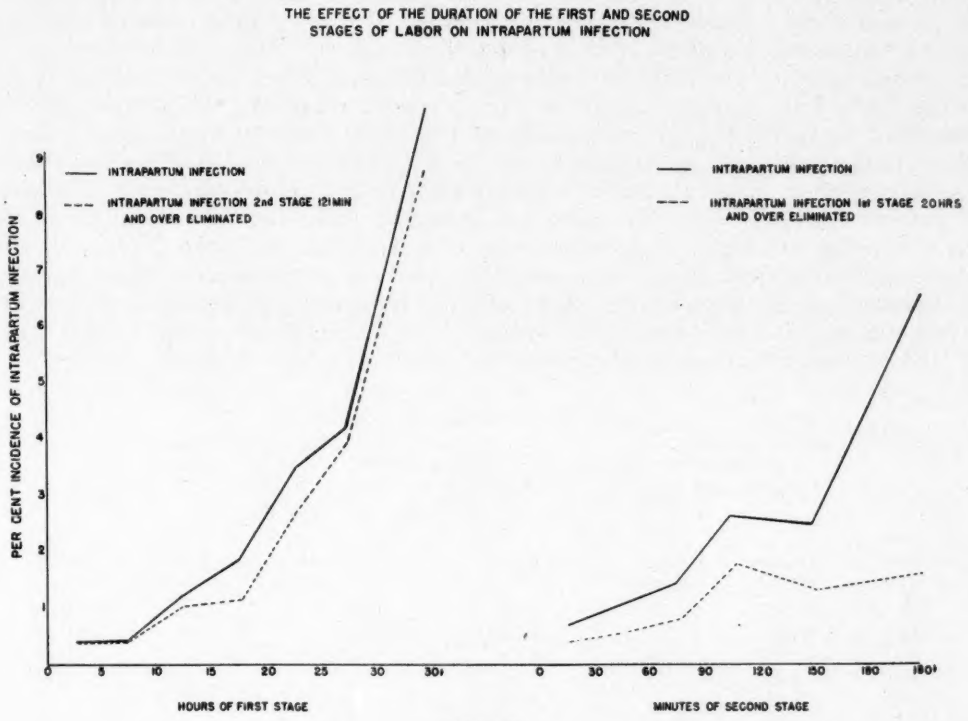
THE EFFECT OF THE DURATION OF THE FIRST AND SECOND STAGES OF LABOR ON INTRAPARTUM INFECTION
PER CENT INCIDENCE OF INTRAPARTUM INFECTION
INTRAPARTUM INFECTION
INTRAPARTUM INFECTION 2nd STAGE 121 MIN AND OVER ELIMINATED
INTRAPARTUM INFECTION
INTRAPARTUM INFECTION 1st STAGE 20 HRS AND OVER ELIMINATED
HOURS OF FIRST STAGE
MINUTES OF SECOND STAGE

Fig. 8.

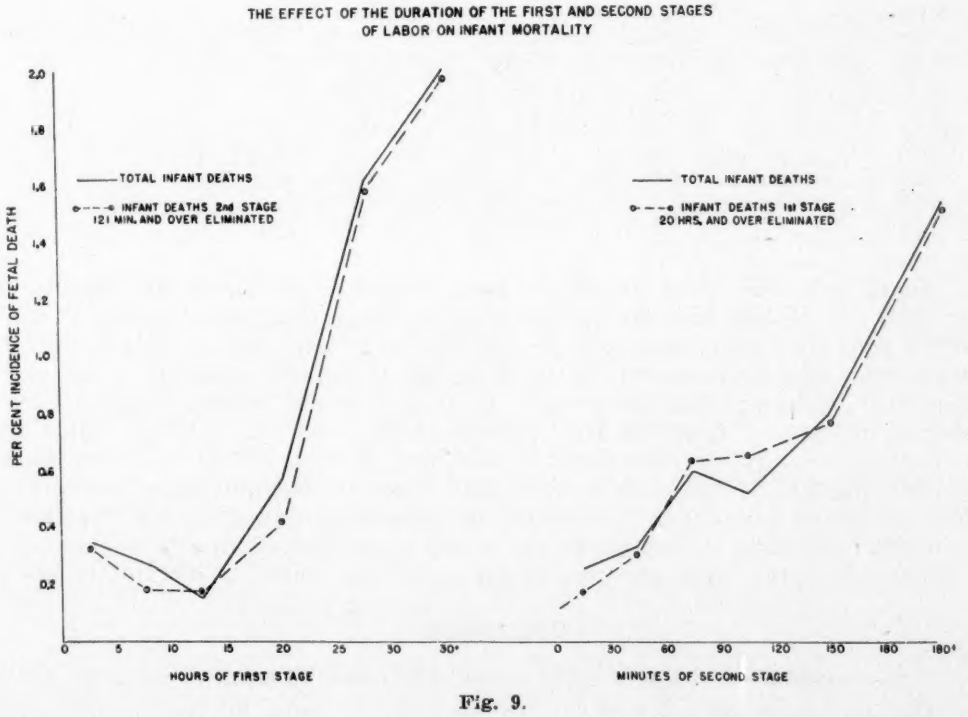
THE EFFECT OF THE DURATION OF THE FIRST AND SECOND STAGES OF LABOR ON INFANT MORTALITY
PER CENT INCIDENCE OF FETAL DEATH
TOTAL INFANT DEATHS
INFANT DEATHS 2nd STAGE 121 MIN. AND OVER ELIMINATED
TOTAL INFANT DEATHS
INFANT DEATHS 1st STAGE 20 HRS. AND OVER ELIMINATED
HOURS OF FIRST STAGE
MINUTES OF SECOND STAGE

Fig. 9.

to be more effective in influencing this complication than does prolongation of the second stage. However, respective removal of unduly long cases of first and second stages still produces curves of a similar nature. It can therefore be said that prolongation of both the first and second stages of labor has an individual and definite effect upon the occurrence of puerperal febrility, the former having somewhat more weight. In the study of Fig. 8, a different result can be seen. This chart deals with intrapartum infection. Both the first and second stages would appear to effect the occurrence of such fever. However, when the cases of second stage of over two hours are removed from the first-stage data, the curve for the incidence of intrapartum fever remains the same. When a like manipulation is applied to the figures for duration of the second stage, namely, the removal of all cases of first stage of over 20 hours, the resulting curves are divergent, and it can therefore be stated that prolongation of the second stage of labor has no effect upon the occurrence of intrapartum infection.

TABLE VII. FETAL MORTALITY

| ACCORDING TO THE DURATION OF THE SECOND STAGE OF LABOR SECOND STAGE OF 120 MINUTES OR MORE ELIMINATED | | | | | | |
|---|---|---|---|---|---|---|
| MINUTES SECOND STAGE | NO. OF CASES | FETAL DEATHS | PERCENTAGE | NO. OF CASES WITH FIRST STAGE LESS THAN 20 HOURS | FETAL DEATHS | PERCENTAGE |
| 0-30 | 7,183 | 18 | 0.25 | 6,695 | 11 | 0.16 |
| 31-60 | 3,101 | 11 | 0.35 | 2,759 | 8 | 0.29 |
| 61-90 | 1,313 | 8 | 0.61 | 1,125 | 7 | 0.62 |
| 91-120 | 746 | 4 | 0.54 | 623 | 4 | 0.64 |
| 121-180 | 645 | 7 | 1.09 | 520 | 4 | 0.77 |
| 181+ | 389 | 6 | 1.54 | 321 | 5 | 1.56 |
| ACCORDING TO THE DURATION OF THE FIRST STAGE OF LABOR SECOND STAGE OF 120 MINUTES OR MORE ELIMINATED | | | | | | |
| HOURS FIRST STAGE | NO. OF CASES | FETAL DEATHS | PERCENTAGE | NO. OF CASES WITH SECOND STAGE 120 MINUTES | FETAL DEATHS | PERCENTAGE |
| <5 | 3,372 | 12 | 0.36 | 3,258 | 11 | 0.34 |
| 5-9 | 4,813 | 13 | 0.27 | 4,506 | 8 | 0.18 |
| 10-14 | 2,533 | 4 | 0.16 | 2,287 | 4 | 0.17 |
| 15-19 | 1,300 | 10 | 0.77 | 1,138 | 7 | 0.61 |
| 20-24 | 623 | 1 | | 548 | 0 | |
| 25-29 | 309 | 5 | 1.62 | 257 | 4 | 1.6 |
| 30+ | 422 | 9 | 2.13 | 365 | 7 | 1.92 |

Finally, in the study of infant mortality which is shown graphically in Fig. 9, it can be seen that the infant death rate increases from 0.25 per cent to 1.5 per cent with prolongation of the second stage, and from 0.35 per cent to 2.1 per cent with prolongation of the first stage. Removal from these curves of cases with prolonged first stage and prolonged second stage, respectively, in order to procure a "pure culture" picture of first and second stage yields unchanged curves. It can, therefore, be said that prolongation of the first stage and prolongation of the second stage both have an independently deleterious effect on infant mortality. This effect becomes apparent when the first stage has lasted more than 20 hours. In the second stage the fetal mortality increases progressively with time and reaches a significant point after 150 minutes.

## Conclusions

1. The median duration of labor is slightly under 20 minutes for multiparas and slightly under 50 minutes for primiparas. There is no significant racial difference between white and Negro.

2. While borderline contractions of the pelvis do not affect the duration of the second stage in multiparas there is a slight prolongation of the second stage in primiparas.

3. The posterior positions of the fetal head cause definite prolongation of the second stage. Where the head remains persistently posterior, the duration of the second stage is more than doubled.

4. There is a correlation between the duration of the first and of the second stages of labor up to 20 hours of the first stage. Beyond this point, the duration of the first stage does not significantly affect the duration of the second stage.

5. Prolongation of both the first and the second stages of labor has a definite influence upon postpartum hemorrhage, the influence of prolongation of the second stage being somewhat greater.

6. Prolongation of both the first and the second stages of labor has an influence upon the occurrence of puerperal febrility, the prolongation of the first stage carrying slightly more weight.

7. The occurrence of intrapartum fever is influenced by prolongation of the first stage but not by prolongation of the second stage of labor.

8. Infant mortality rises with prolongation of both the first and the second stages of labor. These two effects operate independently. The first-stage effect is apparent after a duration of 20 hours, while the increase in fetal mortality takes place when the second stage has lasted more than 150 minutes.

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# THE TREATMENT OF BENIGN UTERINE BLEEDING WITH INTRACAVITARY RADIATION

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THE purpose of this presentation is to evaluate the results obtained by the treatment of benign uterine bleeding with intracavitary radiation. On reviewing the early literature concerning this subject one finds a report by William James Morton in the *New York Medical Record,* July, 1903, on "The Control of Uterine Hemorrhage Due to Myomata by X-ray Treatment of the Lesion Through the Lower Abdomen." Later, in October, 1906, two French observers, Oudin and Verdure, also reported their experiences. With the progress of time and with our advancing knowledge of radiant energy, an increasing number of reports are found on the control of uterine bleeding with irradiation, so that today this method of treatment, so free of bad results, becomes increasingly popular.

What are the indications for intracavitary radiation for benign uterine bleeding? We believe that the following criteria are essential for satisfactory results: The patient should be at least 40 years of age, when further childbearing is not to be considered; conservative measures, i.e., hormonal therapy and curettage, should have been carried out unsuccessfully; the patient should be a poor operative risk, due to severe hypertension, cardiac disease, or any other debilitating condition that would render an extensive operative procedure hazardous; a patient at the menopause, who has small uterine fibromas, preferably excluding the submucosal type; a patient fearful of operation—an infrequent indication.

Now, what are the contraindications to this method of therapy? The most important, we feel, is pelvic inflammatory disease, for, if present, radiation may incite the development of parametritis or even peritonitis. Obviously, young women should not be included in this group. The presence of ovarian masses and large uterine tumors is a contraindication. Some believe that intracavitary radiation can be successfully accomplished if the uterine tumor is no larger than the size of a three-months' pregnancy. We feel that with a mass of this size necrosis may set in, regression may not be complete, and the bleeding may continue. Surgical removal in this instance is far preferable. Submucous myomas may or may not be a contraindication. Robert Schroeder has always been of the opinion that this is a definite contraindication due to necrosis of the surface endometrium covering the tumor, with continuation of bleeding and discharge; however, this is not always the

case for we have had successes, but failures frequently do occur. If fundal carcinoma, or a suspicious hyperactive, hyperplastic endometrium is detected at the diagnostic curettage, which is always done, multiple-source radiation is carried out with a greatly increased dosage. A type of uterine bleeding that has received little attention is that associated with blood dyscrasias. The mechanism of this bleeding is at times difficult to explain. The following systemic diseases that may be associated with uterine bleeding are as follows:

1. Acute leukemia, of any variety.
2. Aplastic anemia.
3. Essential thrombocytopenic purpura.
4. Secondary thrombocytopenic purpura.
5. Hereditary hemorrhagic telangiectasis (Osler-Weber disease).
6. Constitutional thrombopathy (von Willebrand's disease).

During the past year an unusual condition known as von Willebrand's disease was observed by a member of our staff. The diagnosis was made after a thorough study by the hematologic department. This condition has a familial tendency and is thought to be due to increased capillary permeability. The hypermenorrhagia was so marked that the young patient became nearly exsanguinated with each menstrual phase. This condition necessitated frequent transfusions associated with the administration of rutin (vitamin P) and vitamin C. The hypermenorrhagia in time decreased to practically normal limits so that the necessity of hysterectomy was eliminated. In all blood dyscrasias a careful pelvic examination is indicated to rule out the possibility of local pathology being the etiological factor for the hypermenorrhagia. Barnes is of the opinion, from his studies, that an individual with a hemorrhagic dyscrasia will not develop hypermenorrhagia without the intermediary of a local pelvic abnormality. From his observation on patients with thrombocytopenic purpura who came to operation for splenectomy, the intra-abdominal pelvic examination showed pathology in the majority of patients and a frequent finding was that of multiple cysts of the ovary. As is obvious, there should be close cooperation between the gynecologist and the hematologist in handling such problems.

## Description of Radiation Technique

After a thorough curettage, frozen sections are then studied to determine the possible presence of malignant disease. If found, the uterus is packed with capsules of radium, sufficient to fill the cavity, and a dosage of 4,500 mg. hr. is then administered. If malignancy is not found, 100 mg. of radium, in tandem, are inserted into the uterine cavity, the filtration being 1 mm. of platinum and irridium; a dosage of 2,000 mg. hr. of radiation is then delivered. The bladder and rectum are well packed away to obviate possible damage. The action of the ray is twofold; the major effect is upon the follicular system of the ovary while the minor is upon the endometrium. The follicular system undergoes degeneration, hyaline changes are noted, and the end result is a corpus albicans, the ovary grossly showing fibrosis and marked diminution in size. The endometrial glands undergo marked degenerative changes so that eventually there is complete loss of the endometrium. Myometrial glands, which

are often seen, also undergo destruction. In individuals with increased radiation sensitivity some superficial necrosis of the myometrium may occur, with a transient discharge of varying degrees. With ovarian degeneration there is evidence of regression of the entire generative system. The vast majority of radiated uteri show very little gross pathology, probably chronic subinvolution with retroversion, beginning descensus being one of the frequent findings.

As will be deduced from the above remarks, the cessation of hypermenorrhea is dependent upon regressive changes in the ovary, with absence of estrogenic effect, and also upon the degeneration of the endometrium. The immediate radiation symptoms are quite mild; minimal nausea is perhaps the most frequent, and there may be some suprapubic discomfort. With the removal of the intrauterine applicator and vaginal pack, the symptoms soon disappear. Postradiation symptoms come on several weeks to a month later and are frequently ushered in with varying degrees of vasomotor disturbances, chiefly seen in the face, neck, and shoulders; associated with these changes, hot flushes may develop. Some observers are of the opinion that the menopausal symptoms produced by radiation are more intense than those appearing after surgical ablation and after the normal physiologic climacteric. This is very difficult to evaluate, for the individual differential is so variable. Consider the pyknic type of patient; as a rule the symptoms will be minimal, requiring only mild sedation; whereas, the tense, neurotic individual of the leptosome type, with a low threshold of pain, will frequently have severe climacteric disorders requiring intensive hormonal therapy for their control. One would deduce that the surgical oophorectomy, with sudden hormonal imbalance, would be more provocative of a severe climacteric than the rather slow ovarian regression produced by radiation. From our observation we do not feel that the symptoms of the climacteric produced by radiation are of sufficient variant to be noteworthy.

An analytic evaluation of 225 patients who received intracavitary radiation for benign uterine bleeding now follows: Of these 50 were discarded due to variation in radiation dosage. The remaining 175 will now be surveyed from various aspects: In this group 170, or 97.1 per cent, of the patients were married, whereas only 5 were single. It is interesting to note that only 18 patients were of the Negro race. A partial explanation for this could be the great frequency of fibroid and inflammatory disease in this race which, in large numbers, necessitates hysterectomy at an early age.

TABLE I. SOCIAL STATUS

| | NUMBER | MARRIED | SINGLE |
|---|---|---|---|
| White | | | |
| Private | 113 | 110 | 3 |
| Service | 44 | 42 | 2 |
| Negro | 18 | 18 | 0 |
| Total | 175 | 170 | 5 |

*Age Incidence.*—The age groups into which these patients fell is of interest. In the fourth decade, 30 to 40 years, there were 11 patients, one being 35 years of age, with severe cardiac disease, who did not respond to curettage and hormonal therapy. The remaining 10 patients were from 38 to 40 years of age. Radiation therapy in this group may be justifiably criticized. On continuing this age study we find that in the fifth decade, 41 to 50 years, there were 113 patients, 64 per cent, and that between 51 to 60 years, there were 48 patients, 27 per cent.

TABLE II. AGE IN YEARS

| | 31-40 | 41-50 | 51-60 | 61-70 | TOTAL |
|---|---|---|---|---|---|
| White | | | | | |
| Private | 7 | 72 | 33 | 1 | 113 |
| Service | 1 | 28 | 13 | 2 | 44 |
| Negro | 3 | 13 | 2 | 0 | 18 |
| Total | 11 | 113 | 48 | 3 | 175 |

## Types of Endometria Found on Curettage and the Incidence of Associated Fibromas

Not so many years ago the majority of cases of benign bleeding were thought to be due to hyperplasia of the endometrium. From our studies we find that although hyperplasia is the most frequent pathological finding, other endometrial types are frequently seen. Proliferative and secretory phases are very often observed and even the atrophic endometrium is not uncommon with benign uterine bleeding. Endometrial polyps are also rather prevalent. In this series of 175 patients, uterine fibromas were encountered in 37 patients, 21.1 per cent; of the 51 patients with hyperplasia, fibroids were encountered in 13, 25.5 per cent. Such evidence of possible hyperestrinism is not uncommon.

TABLE III. ENDOMETRIAL HISTOPATHOLOGY WITH ASSOCIATED MYOMA

| | WHITE | | | | NEGRO | | TOTAL | |
|---|---|---|---|---|---|---|---|---|
| | PRIVATE | | SERVICE | | | | | |
| | NO. | WITH FIBROIDS | NO. | WITH FIBROIDS | NO. | WITH FIBROIDS | NO. | WITH FIBROIDS |
| Menstruating | 1 | | 0 | | 0 | | 1 | |
| Proliferative | 25 | 3 | 11 | 3 | 5 | 2 | 41 | 8 |
| Secretory | 27 | 5 | 5 | 0 | 2 | 0 | 34 | 5 |
| Atrophic | 11 | 1 | 8 | 4 | 0 | 0 | 19 | 5 |
| Hyperplasia | 36 | 7 | 8 | 3 | 7 | 3 | 51 | 13 |
| Polyps | 7 | 0 | 2 | 1 | 0 | 0 | 9 | 1 |
| Insufficient tissue | 3 | 0 | 9 | 2 | 4 | 2 | 16 | 4 |
| No endometrial report | 3 | 1 | 1 | 0 | 0 | 0 | 4 | 1 |
| Total | 113 | 17 | 44 | 13 | 18 | 7 | 175 | 37 |

An analysis of the duration of bleeding is of interest for, as we know, such a condition may exist for many months, being produced by adenocarcinoma, endometrial polyps, and especially by hyperplasia of the endometrium. The examination of the data shows great variation, i.e., one week to more than a year.

TABLE IV. DURATION OF BLEEDING—PRERADIATION

| | LESS THAN 1 MO. | 1 MO. | 2 MO. | 3 MO. | 4 MO. | 6 MO. | 1 YR. | OVER 1 YR. | UNKNOWN |
|---|---|---|---|---|---|---|---|---|---|
| White | | | | | | | | | |
| Private | 31 | 11 | 7 | 11 | 9 | 12 | 8 | 12 | 12 |
| Service | 6 | 3 | 4 | 5 | 2 | 7 | 2 | 12 | 3 |
| Negro | 2 | 1 | 3 | 5 | 2 | 2 | 1 | 2 | 0 |
| Total | 39 | 15 | 14 | 21 | 13 | 21 | 11 | 26 | 15 |

The making of a positive diagnosis in order to rule out malignant disease is the sine qua non. The age of the patient plays no role in precluding a diagnostic curettage, for we have encountered adenocarcinoma of the corpus

in a young woman of 23 years of age when we were clinically certain hyperplasia existed. Biopsy of the cervix is also imperative when the main symptom is serosanguineous discharge.

How effective is intracavitary radation? Every patient in this survey of 175 patients received the same amount of radiation, namely, 2,000 mg. hr., the filtration being platinum and iridium, as stated above. The duration of bleeding, after its application, is the chief index of its efficiency. Immediate cessation after radiation occurred in 117 patients; however, a continuation of normal menstruaton for varying lengths of time was not uncommon. Seven patients had a return of bleeding in two weeks and then ceased. Thirty-three had one normal menstrual period, at the usual time, with no reappearance. Eight patients had four menstrual periods and one patient menstruated for 18 months and then ceased. The continued menstruation indicates varying degrees of susceptibility of the follicular system to the radium ray and possible estrogenic stimulation from the adrenal.

TABLE V. DURATION OF BLEEDING—POSTRADIATION

| | IMMEDIATE CESSATION | 2 WK. | 1 MO. | 4 MO. | 6 MO. | 1 YR. | OVER 1 YR. |
|---|---|---|---|---|---|---|---|
| White | | | | | | | |
| Private | 75 | 4 | 24 | 5 | 0 | 0 | 0 |
| Service | 32 | 1 | 7 | 2 | 0 | 0 | 0 |
| Negro | 10 | 2 | 2 | 1 | 0 | 0 | 1 (18 mo.) |
| Total | 117 | 7 | 33 | 8 | 0 | 0 | 1 |

There was no mortality incidence and the complications noted were the development of a septic temperature in one patient; this was attributed to a transfusion reaction; the remaining patient developed a cellulitis of the left parametrium which was of several weeks' duration. As stated above, leukorrhea may occur following intracavitary radiation due to localized degenerative changes; this symptom, as a rule, is of transient duration. The results of a follow-up study on the successfully treated symptom-free patients are shown in Table VI.

TABLE VI. FOLLOW-UP OF SYMPTOM-FREE PATIENTS

| TIME | PATIENTS |
|---|---|
| 6 mo.-5 yr. | 70 |
| 5 yr.-10 yr. | 64 |
| 10 yr. and over | 32 |

## Radiation Failures

There were 9 patients who fell into this category, all having received 2,000 mg. hr. of radium. The failure in 6 was probably due to associated fibromas, the submucous type predominating. Hysterectomies were performed on 4 of this group. The remaining one developed adenocarcinoma 9 years later. She was given intracavitary radiation, 4,500 mg. hr., and a panhysterectomy will be carried out in the near future if her poor cardiac condition improves sufficiently. The three remaining failures were not associated with uterine fibromas, but probably were brought about by the reactivation of dormant primordial follicles or estrogenic stimulation from the adrenal. One of this group required an additional 1,200 mg. hr. of radium to control the recurrent bleeding which developed one year following the initial radiation of 2,000 mg. hr. The endometrium was of the atrophic type. This patient

has been followed since 1933 with no return of symptoms. One patient had recurrent bleeding, slight in amount, for 18 months, brought about by the use of stilbestrol. The minimal bleeding from a proliferative endometrium ceased with withdrawal of medication. The remaining patient had attacks of recurrent bleeding; three curettements showed no evidence of malignancy and there has been no recurrence of bleeding for a period of nine months.

Uncorrected failures show an incidence of 5.1 per cent. If the six patients with fibroid disease are excluded, due to the expectancy of cure being remote, the incidence of failure is 1.7 per cent.

TABLE VII. RADIATION FAILURES

| DIAGNOSIS | RADIUM 2,000 MG. HR. | BLEEDING RECURRED | OPERATION | PRESENT STATUS |
|---|---|---|---|---|
| 1. Atrophic | 7/27/44 | 7/ 4/47 | Slight bleeding Operation unnecessary | Living and well |
| 2. Atrophic | 6/16/47 | 3/ 9/49 | Curettage No endometrium | Living and well |
| 3. Atrophic | 3/ 8/32 | 6/ 1/33 | 1,200 mg. hr. radium | Living and well |
| 4. Fibroid | 10/26/39 | 5/11/40 | Hysterectomy | Living and well |
| 5. Fibroid | 8/ 7/46 | 2/ 6/48 | Hysterectomy | Living and well |
| 6. Fibroid | 9/22/47 | 7/16/48 | Hysterectomy | Living and well |
| 7. Fibroid | 8/28/47 | 9/21/48 | Hysterectomy | Living and well |
| 8. Fibroid | 8/15/42 | 10/ 2/46 | Slight bleeding Operation unnecessary | Living and well |
| 9. Fibroid | 10/24/40 | 9/ 1/49 | Curettage Adenocarcinoma | Under treatment |

## Incidence of Malignancy Following Intracavitary Radiation

In a review of the literature, a number of articles are found on the radiation therapy of uterine bleeding, and several authors are of the opinion that this radiation tends to increase the incidence of adenocarcinoma of the uterine body. We are not in accord with this view, for we have encountered only one malignancy in this series of 225 patients, this developing 9 years following radiation and this incidence is far less than the normal expectancy. Figs. 1 and 2 are illustrative.

TABLE VIII. STATISTICAL STUDY OF PATIENT FOLLOW-UP

| AGE GROUP (YEARS) | TOTAL PATIENTS | TOTAL PERSON YEARS FOLLOWED | MEAN NO. YEARS FOLLOWED |
|---|---|---|---|
| 15-19 | 1 | 15 | 15.0 |
| 20-24 | 0 | 0 | |
| 25-29 | 0 | 0 | |
| 30-34 | 1 | 9 | 9.0 |
| 35-39 | 11 | 71 | 6.4 |
| 40-44 | 51 | 394 | 7.7 |
| 45-49 | 78 | 452 | 5.9 |
| 50-54 | 54 | 315 | 5.8 |
| 55-59 | 18 | 91 | 5.0 |
| 60-64 | 10 | 42 | 4.2 |
| 65-69 | 1 | 1 | 1.0 |
| All ages | 225 | 1,390 | 6.2 |

A vital statistical study has been carried out on this series by Dr. Ross Cameron, Chief of the Cancer Division of the Public Health Department of the State of Maryland, and his analytical table is given in Table VIII. It will be noted that there were 225 patients who received treatment with radium for vaginal bleeding. These individuals were observed for a total of 1,930 person years, or 6.2 years per person. Dr. Cameron's remarks follow:

"It has been estimated that the normal expectancy of cancer in persons in the above age group is 2.5 cases per 100 population. In this series there was one case in 225 persons, a rate of 0.44 case per 100 population, which is significantly less than the normal expectancy."

It seems clear, therefore, that in our patients radium did not result in increasing the number of cancer cases above the normally expected rate; on the contrary, the rate was lower than would have been expected.

It will be noted that one patient is in the age group 15 to 19 years; this patient received 560 mg. hr. of radium, which was not intended to produce castration but only to normalize the menstrual cycle. This proved successful. The patient has been followed for 15 years and is entirely well.

In a recent article appearing in the British literature, John F. Foulkes reports a study of 91 patients with uterine bleeding treated by intracavitary radiation. He is of the opinion that this method of therapy does not augment the severity of climacteric symptoms or leukorrhea and, of especial interest to us, no case of postradiation cancer was encountered. A number of authors, Luker, Corscaden, Speert and Peightal, and others, seem to be of the opinion

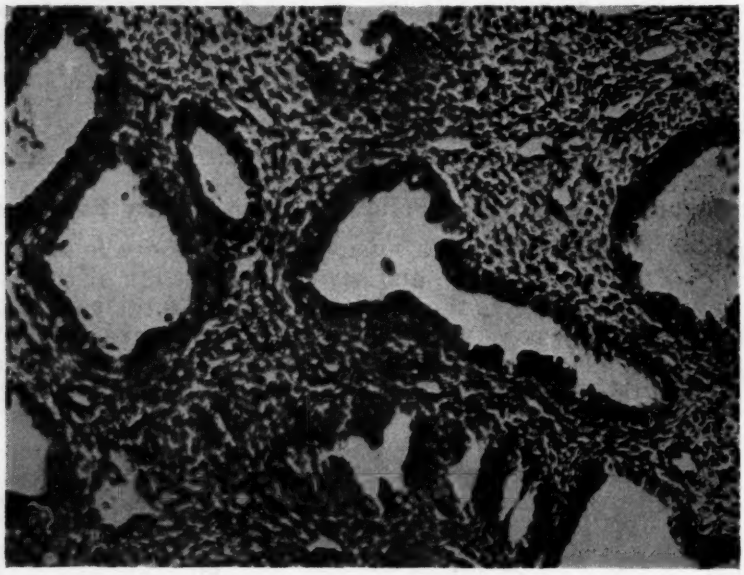

Fig. 1.—R. E., white, aged 60 years. Curettage Oct. 27, 1940. Endometrial hypoplasia.

that intracavitary radiation tends to increase the incidence of corporeal cancer. The appearance of these growths which they report ranges from 2 to 3 years postradiation, up to 11 years. It would seem more logical to deduce that lesions found a comparatively short time after radiation existed at the time of treatment. Scheffey is of this opinion, and in his study of 124 cases of fundal neoplasm he found 13 of them had received previous radiation for a supposedly benign condition. In our study of adenocarcinoma of the uterine body, only one patient out of 110 had received previous radiation for a supposedly benign condition. In connection with this study, one finds in the literature statements that are somewhat difficult to support, namely, that patients with excessive bleeding at the preclimacteric are more disposed to the development of cancer. As is well known, considerable variation in the amount of bleeding exists at this time. In our experience, the more copious bleeding is frequently encountered in multiparas witth subinvoluted uteri which contain

an increased formation of elastic tissues as seen in multiple pregnancies. In our recent study of corporeal cancer, we found that 64.6 per cent of the patients had borne children. If excessive climacteric bleeding is the expression of subinvolution due to multiple pregnancies, then we are in accord that cancer may develop more frequently when preceded by this bleeding symptom. Variation in endocrine imbalance is also a factor of importance.

Peightal deduces from his study of material at the Roosevelt Hospital that the incidence of corpus carcinoma has greatly increased. However, our records at the Hospital of the University of Maryland show no change during the past five years. This author, and others, are of the opinion that carcinoma of the endometrium is exceedingly rare following surgical castration, which is contrary to the findings following irradiation. He ascribes this difference, in part, to the continued production of estrogens by the ovaries which have been subjected to irradiation. This is difficult to prove; however, our histologic studies on radiated ovaries do show residual follicular elements, the majority of which are undergoing regression. This observation will be considered in more detail later on.

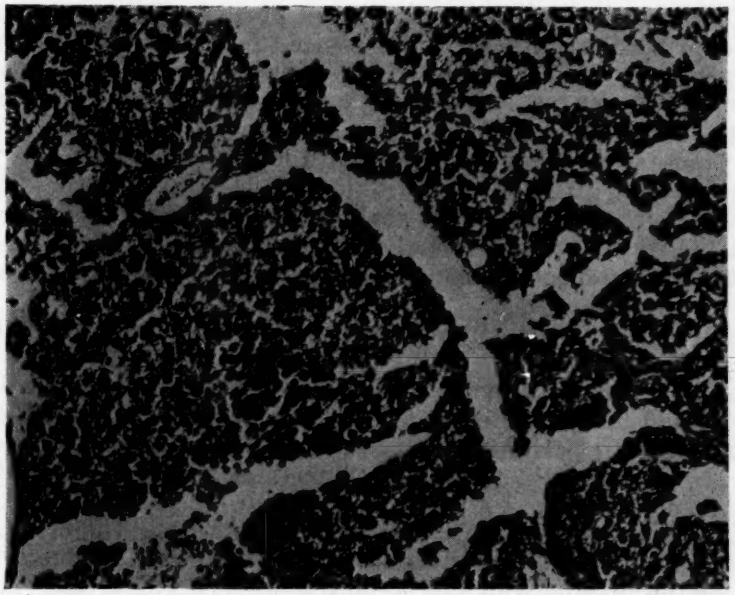

Fig. 2.—R. E., white, aged 69 years. Curettage Nov. 25, 1949. Adenocarcinoma of the fundus, Grade IV.

In our study of 175 patients with uterine bleeding and treated with intracavitary radiation of 2,000 mg. hr., 117 of these had abrupt cessation of bleeding. With this sudden cessation of bleeding one would surmise that complete disintegration of the follicular apparatus had taken place, although this cannot be assured from the following histologic observations. Due to continuation of bleeding after intracavitary radiation, hysterectomies and bilateral salpingo-oophorectomies were carried out on 4 patients who had submucous myomas. On microscopic examination, the ovaries showed residual viable follicular elements even after 2,000 mg. hr. of radium. The interval between the radiation and operation varied from 4 weeks to 18 months. The lutein and granulosa cells showed varying degrees of regression, although some were surprisingly normal. These delayed regressive cellular changes may have been somewhat induced by the associated fibroma, thus causing a diminution of

radiant energy delivered to the ovary, the intervening fibrous mass acting as a filter. Primordial follicles were observed and appeared very similar to those seen in the nonradiated ovary. From these histologic findings it is difficult to believe that the abrupt cessation of uterine bleeding occurring in 117 patients was brought about by sudden and complete cellular regression of the follicular system. However, to my knowledge, this has been the usual interpretation. It is possible that radiation caused sufficient cellular changes, even of a minimal degree, to induce hormonal imbalance, with resulting endometrial suppression, thus causing cessation of bleeding.

## Effect on Endometrium

As is well known, the onset of flushes, the prime index of ovarian waning, does not occur immediately after radiation but, as a rule, weeks or even months later. During this interval, tissue regression of the follicular elements is taking place with a corpus albicans being the terminal stage.

The postmenopausal patients who had adenocarcinoma of the fundus, with preoperative radiation of 4,500 mg. hr., showed, as expected, complete ovarian regression. However, when the patient was preclimacteric it was not uncommon to find primordial follicles which seemed in the realm of normalcy. No typical hyperplasia of the endometria in these removed uteri was observed. These observations are of considerable interest, and further studies on a large source of material would be informative.

Two of our failures, not associated with fibroid pathology, had recurrence of vaginal bleeding; this was attributed to the rejuvenation of dormant primordial follicles, these elements being the most resistant. We must not forget that the cortex of the adrenal is another source of estrogens that plays an important role, especially after the menopause, and may be a factor in producing recurrent bleeding.

A recent communication from Novak is here of especial interest as it concerns the proliferative changes of the endometrium probably due to estrogenic stimulation arising in the adrenal. He describes a patient with benign uterine bleeding who had had a bilateral oophorectomy performed a number of years ago, and after a long period of amenorrhea bleeding returned. She was then seen by Dr. Novak who did a diagnostic curettage and found a marked hyperplasia of the endometrium. A laparotomy followed, and after careful search no ovarian tissue was discovered, nor was a granulosa-cell tumor found; as the uterus was definitely enlarged it was removed. Marked uterine fibrosis with thickening of the uterine wall and extensive hyperplasia of the endometrium was found.

## Summary

In this series of patients with benign bleeding treated with intracavitary radium, we have shown that the procedure is simple, safe, and the results excellent. It is imperative that patients selected for this type of therapy show no evidence of pelvic inflammatory disease, no large uterine fibromas or ovarian tumors. Submucous fibroids may be a contraindication to intracavitary radiation. Patients should be at least 40 years of age.

A survey of the series of 175 patients, all of whom received 2,000 mg. hr. of radium, shows that immediate cessation of bleeding was encountered in 117; of the remaining, menstruation continued from 1 to 4 months, one patient menstruating for 18 months. Of the 9 failures, 5 had fibromas and, of the remaining 3, one was due to stilbestrol and the other 2 due to probable resur-

gence of follicular activity due to adrenal stimulation. Uterine bleeding associated with blood dyscrasias should receive more attention. A patient with von Willebrand's disease is here reported.

A diagnostic curettage is of the greatest importance. If no malignancy is found an intracavitary application of radium, 100 mg. in tandem, is carried out, filtration is of platinum and iridium, 2 mm. lead equivalent, dosage 2,000 mg. hr. The action of the ray is twofold: the major effect is upon the follicular system of the ovary and the minor upon the endometrium; the end result being complete regression of the ovary in the vast majority of cases and destruction of the endometrial glands.

Immediate symptoms include minimal nausea, which is relieved when the radium is removed.

Postradiation symptoms may consist of transient vaginal discharge arising from degenerative changes in the myometrium. Flushes of the climacteric do not seem to be more pronounced than those occurring after the normal menopause or after surgical ablation. It is thought by some that intracavitary radiation causes a lessening of libido; again this problem is extremely difficult to evaluate as so many factors come into play.

It is interesting to note that in this survey there were only 18 patients of the Negro race. A partial explanation may be due to the great frequency of fibroid and inflammatory disease in this race, which necessitates hysterectomy at a comparatively early age in large numbers. On reviewing the age groups of patients treated, we find 91.9 per cent were between 41 and 60 years of age.

We find on studying the types of endometrium that the proliferative predominates, 92 cases falling in this category. The frank hyperplasias were 51 in number.

It is the apparent belief of some authors that intracavitary radium tends to increase the incidence of adenocarcinoma developing in the uterine corpus, the growths developing 9 to 10 years following radiation. We are not in accord with this view for we encountered only 1 malignancy in reviewing 225 patients. A vital statistical study carried out by the U. S. Public Health on 225 patients, all treated with radium, showed an incidence of 0.44 case per 100 population, which is significantly less than the normal expectancy, which is 2.5 cases per 100 population. Quoting Dr. Ross Cameron, who made the survey, "It seems clear, therefore, that in our patients treated, radium did not increase the number of cancer cases above the normally expected rate. On the contrary, the rate was lower than would have been expected."

Residual follicular elements were noted in ovaries removed from 4 weeks to 18 months post radiation. Fairly normal cells were observed although regressive changes were prominent.

A follow-up study on the successfully treated patients showed 32 patients alive and well after 10 years or more; 64 patients alive and well after 5 years and the remaining 70 patients showed no abnormality less than 5 years after treatment.

Uncorrected failures show 5.4 per cent. If the 6 patients with fibroid disease are excluded, due to the expectancy of cure being remote, the incidence of failure is 1.7 per cent.

No death occurred.

## Conclusions

The proper selection of patients for this type of therapy is most essential. The advantages are: (1) excellent results; (2) no operative shock; (3) no mortality; (4) rare sequelae; (5) no operative discomfort; (6) shorter hospitalization.

The main disadvantages, according to some, are cessation of ovarian activity, and the possible increase of adenocarcinoma following radiation. We do not believe that radiation of the uterine corpus tends to increase the incidence of adenocarcinoma, for we found one adenocarcinoma developing nine years after radiation; which is less than the normal expectancy according to our vital statistical study.

If the patient is 40 years old, or older, the absence of ovarian activity is of little consequence.

Vaginal hysterectomy is preferred by a number of gynecologists; however, we feel that this is an unnecessary surgical procedure.

Some are of the opinion that patients with benign uterine bleeding at the menopause should have the uterus removed, for it has served its childbearing function and therefore no reason for its maintenance exists. This deduction seems of questionable value, for if the thought was carried through every menopausal uterus, having served its childbearing function, should be removed for it too may be the focus for a developing carcinoma.

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MEDICAL ARTS BUILDING

# COMBINED VAGINAL AND ABDOMINAL PLICATION AND CYSTOPEXY FOR URINARY STRESS INCONTINENCE*

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THIS procedure attempts to combine in one operation all of the principles of corrective surgery that have been demonstrated to be necessary by the majority of observers. Pelvic surgeons will recognize a composite technique and approach to the problem that incorporates many familiar and several less common operations. There is no attempt to credit anyone for priority or originality. The literature on this subject reveals no feature of this operation that was not performed by some one of our predecessors many years ago. The technical details of each step of the procedure have been changed where modifications promised a better result.

When rigid criteria of cure of incontinence are applied to patients after a simple anterior wall plastic, most vaginal surgeons have a disturbingly high percentage of patients who still "leak a little," "are better but have to be careful on occasions," or are "worse than before the operation." In evaluating this operation the patients who were dry under all conditions were listed as cured and those who lost urine on stress at any time were considered failures. This combined procedure promises to eliminate the majority of failures not only because of its effectiveness in the recurrent cases but also by its application to primary cases where the risk of failure by a simple repair is very high.

The logic for each step of this operation was determined by radiologic study of the position of the bladder neck and urethroscopic observation of its function in normal and incontinent women. The female urethra is a muscular sleeve about 4 cm. in length which keeps it walls approximated by its inherent tone. It normally can resist the average intravesical pressures to which it is subjected plus any increase caused by sudden increased abdominal pressure. The mechanism of voiding is not completely understood neurologically but certain facts are clear after study of the bladder neck through a water urethroscope. Micturition is initiated by voluntary straining plus an over-all contraction of the bladder to complete the act. Some reflex allows distention and relaxation of the organ. Urination may be voluntarily restrained by elevating the bladder neck through contraction of the puborectalis. Any discussion of an internal and external sphincter, while still haunting the textbooks and literature, is mythological since no such structures exist.

*Read before the New York Obstetrical Society, Dec. 11, 1951.

Patients with stress incontinence demonstrate a forward and downward displacement of the bladder neck in relation to the inferior border of the symphysis. This results in a funneling of the bladder neck and proximal one-third of the urethra. The bladder neck and urethra are, in effect, incorporated into the bladder cavity. In continent patients the normal tone of the urethra keeps its walls approximated and its caliber reduced sufficiently to withstand ordinary increases in intravesical pressure caused by stress. In incontinent patients this is not true since this muscular sleeve normally offers only slight resistance and it takes but little anatomical distortion to make it incompetent.

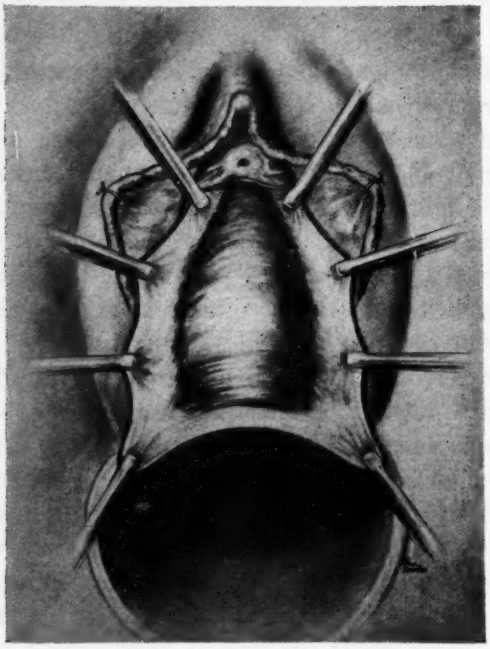

Fig. 1.—The full thickness of the vaginal wall is opened retrograde.

X-ray and urethroscopic observations on many patients indicate that the further forward the bladder neck lies anatomically the less excursion forward will be necessary to cause funneling of a degree inconsistent with continence. This may happen because the urethra is fixed in an abnormal position by scars from paraurethral lacerations during delivery or by previous vaginal surgery. The position of the bladder neck must be determined accurately before an operation can be intelligently planned for its reposition. When doubt exists some type of urethrogram is indicated in the preoperative study of the patient.

The following principles of operative correction are carried out in this operation. The urethra is mobilized and all scar tissue lysed that fixes it in an abnormal position. Symmetry is important. It is then plicated longitudinally to reduce its caliber and increase its effective length in so far as this can be done during the vaginal stage of the operation. The bladder neck is then plicated specifically. From an abdominal approach in the space of Retzius the bladder neck is then plicated 180 degrees opposite the vaginal plication. This

very effective approach completes the reduction of any funneling of the bladder neck. The bladder neck is then reposed behind the symphysis by a simple suprapubic suspension to the periosteum of the symphysis.

## Operative Technique

The labia minora are retracted and sutured to the skin. A preliminary curettage is done if the ureterus or cervical stump is present. Allis clamps are placed on each side of the external meatus and the vaginal wall opened in retrograde fashion. If the meatus is gaping and displaced forward, particularly if confirmed by a urethrogram, the distal urethra is sharply dissected free of all adhesions and the remains of the attachments called the urogenital diaphragm. The shorter the length of the urethra the more extensive must be the mobilization in all directions in order to create a more effective length later in the operation (Fig. 1).

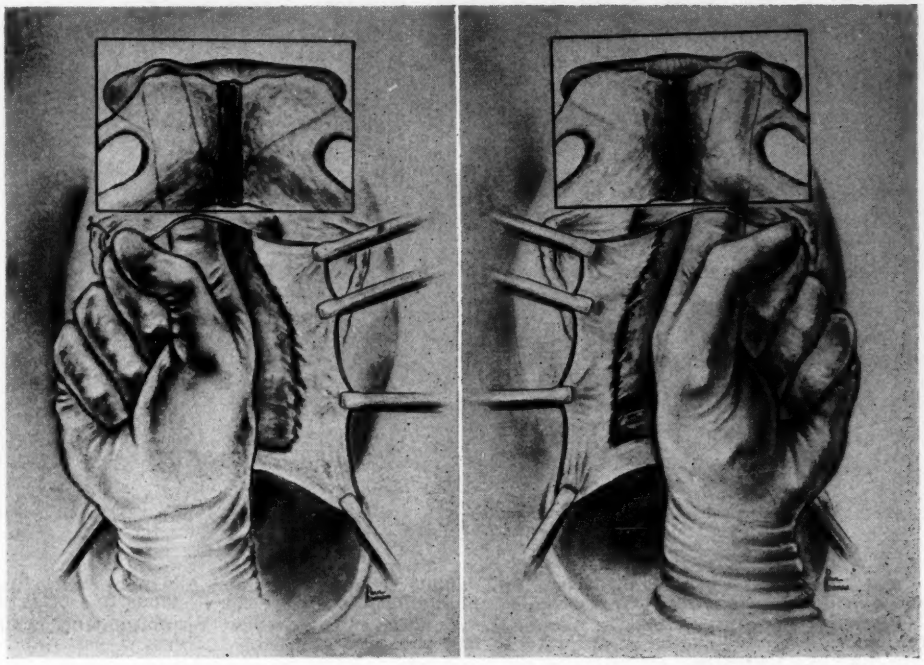

Fig. 2. Fig. 3.

Fig. 2.—The right side of the urethra is mobilized by the operator's right index finger which is introduced into the lateral recess of the space of Retzius.

Fig. 3.—The left side of the urethra is similarly mobilized using the left index finger.

The index finger of the right hand is then introduced between the urethra and the periosteum of the pubis just lateral to the symphysis on the right side. By firm pressure and a rolling motion toward the urethra the finger is made to enter the right lateral recess of the space of Retzius (Fig. 2). The ureters will be pushed away as they lie on the superior surface of the levators. In this dissection all adhesions, fibers of the puborectalis, plus the extensions of the obturator fascia over the levators are lysed and the urethra mobilized. An identical maneuver is done on the left side using the left index finger (Fig. 3). Any further dissection is done to mobilize the urethra and give it together with the bladder neck as symmetrical and appearance as possible. Since the undistorted and exact approximation of its walls is the objective, by which it

obtains continence, it is essential that both its dissection and plication be as symmetrical as possible. If excessive bleeding is encountered from the prevesical plexus a sponge is placed on either side and removed during the abdominal stage of the procedure.

A full-length plication of the urethra, bladder neck, and bladder is now done with interrupted sutures of 00 chromic catgut. The extent of this varies from patient to patient but a free, symmetrical urethra and bladder neck should result. Three on-end-mattress sutures of 0 chromic catgut are then taken in the bladder neck (Fig. 4). The operation was planned as to the number, position, and caliber of sutures that might be used without causing necrosis of the parts.

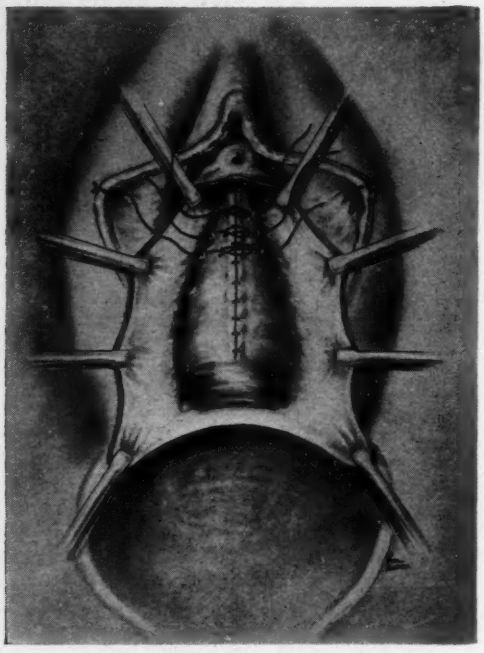

Fig. 4.

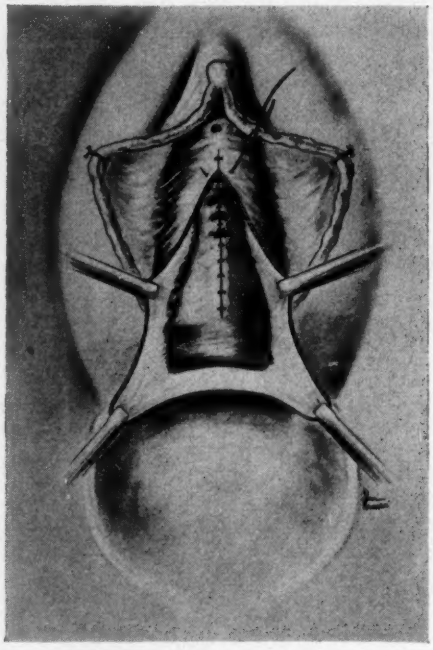

Fig. 5.

Fig. 4.—The urethra, bladder neck, and bladder base are plicated for their entire length. Three on-end-mattress sutures are placed at the bladder neck over the previous line of sutures.

Fig. 5.—The vaginal wall is trimmed conservatively to prevent retraction and bridging of the pubic arch by mucosa inadequate to line the area.

We advise against any additional special or favorite sutures of the individual operator added to the above since considerable plication will be done from the abdominal approach. The creation of dense scar tissue at the bladder neck by coarse suture material in order to hold things up is ill advised since scar tissue is notoriously weak when subjected to stress. A simple water urethroscope is valuable to study the result. When directly visualized the posterior wall is seen to be elevated but the reduction in caliber of the bladder neck is not pronounced. While the posterior or vaginal plication of the urethra, bladder neck, and base may not cause an extensive narrowing of the bladder neck it serves an additional purpose. The plication strengthens and fixes the entire bladder base so that the plication from the anterior aspect can be most effective.

The edges of the vaginal wall are conservatively trimmed as indicated and closed with interrupted sutures of 00 chromic catgut (Fig. 5). Anterior vaginal walls will be seen where several attempts at cure of the condition have been made with further trimming, in each instance, of an already retracted wall.

Since the pubic arch is a roughly triangular space one must leave enough wall to curve around and line the arch. If too much is removed the remaining vaginal wall will have to stretch across space to the descending rami. As a characteristic of the healing process, it will tend to attach itself to surrounding tissues and close in the dead space. The surrounding tissue is the bladder base which may be drawn down despite all efforts to replace it backward and upward. It is an important point that one should leave enough vaginal wall to prevent retraction and in most instances this means no trimming of the vaginal wall. Some patients may require other vaginal surgery in conjunction with the above and this is done according to the individual technique of the operator. A two-inch gauze pack is placed in the vagina and a small French catheter in the bladder. This is placed after the abdominal stage of the operation if a cystotomy is contemplated.

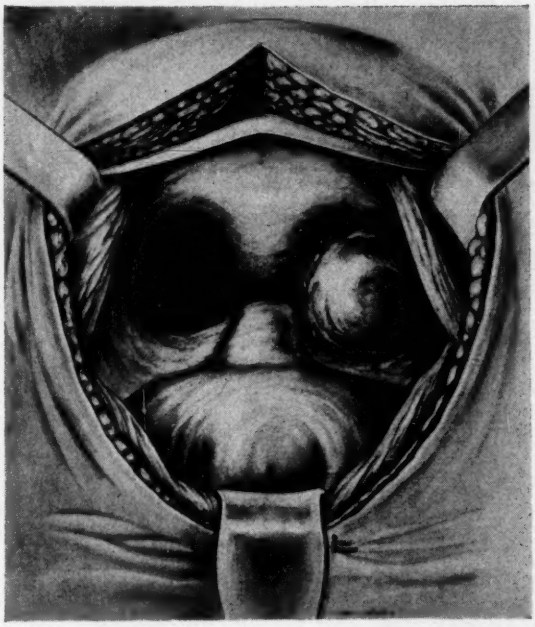

**Fig. 6.—The space of Retzius is entered abdominally and the landmarks identified.**

The preferred abdominal incision is a low Pfannenstiel but if a lower midline or rectus scar exists these can be excised and these other approaches used. In extremely obese patients with a deep symphysis and funnel pelvis the rectus muscles may be detached from the symphysis by cutting the tendons about 2 cm. from their insertions. This gives very ample room to work in the space of Retzius but is only occasionally necessary. With the recti retracted laterally the dome and anterolateral aspects of the bladder are exposed (Fig. 6). The index and middle fingers then straddle the bladder anteriorly and almost by the weight of the hand the bladder, bladder neck, and urethra are detached from their fragile areolar connections with the symphysis. The tips of the fingers will now meet the areas entered from below or the sponges left for hemostasis. Rarely a bleeding point not controlled by the sponges must be ligated but this is as simple from this approach as it is almost technically impossible from the vaginal aspect. The temptation to sponge the periosteum vigorously for minor bleeding should be avoided since this causes pain later. Minor bleeding is occasionally seen and controlled by a sponge in each lateral recess during the next stage of the operation.

Fig. 7.

Fig. 8.

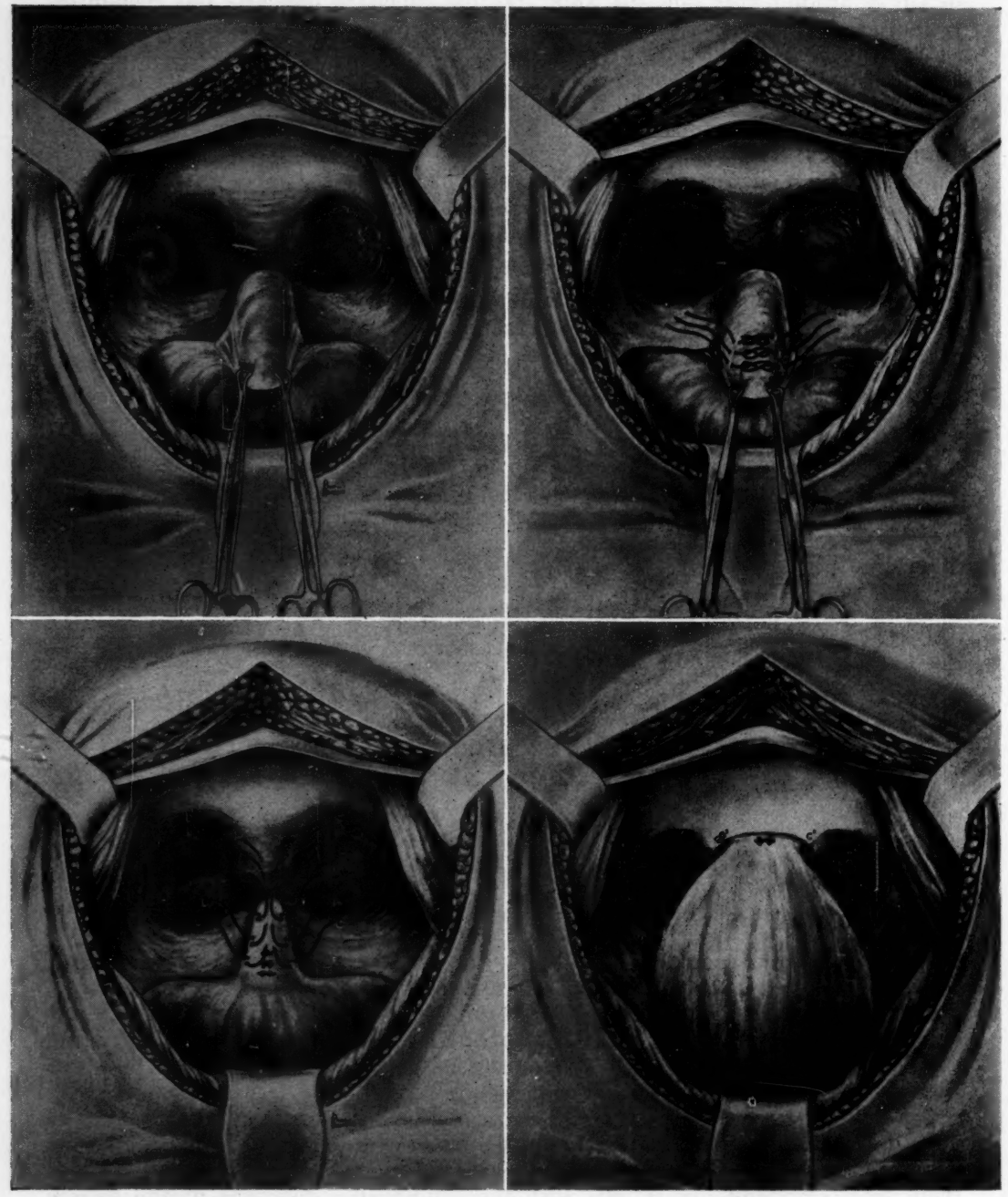

Fig. 9.

Fig. 10.

Fig. 7.—Traction on the bladder neck clearly outlines this structure and the anterolateral walls of the bladder.

Fig. 8.—The bladder neck is plicated anteriorly by three on-end-mattress sutures. These sutures of 00 chromic catgut perforate the muscular wall of the bladder.

Fig. 9.—A simple suprapubic suspension is done with 0 chromic catgut. This replaces the urethra and bladder neck well behind the symphysis.

Fig. 10.—Drains are usually placed in each lateral recess before the incision is closed.

Two Babcock clamps are then placed on the anterior wall of the bladder just above the bladder neck (Fig. 7). By gentle traction on the clamps the bladder neck and proximal urethra are fixed by the first assistant. By the use of sharp and blunt dissection the areolar tissue and adventitia are removed from this portion of the bladder before the anterior plication is done. The plication sutures go directly into the bladder wall. Three on-end-mattress sutures are placed at the bladder neck to reduce its caliber and funneling (Fig. 8). Note that these are directly opposite the vaginal plication sutures. If any doubt exists as to their effectiveness a cystotomy may be done and the bladder

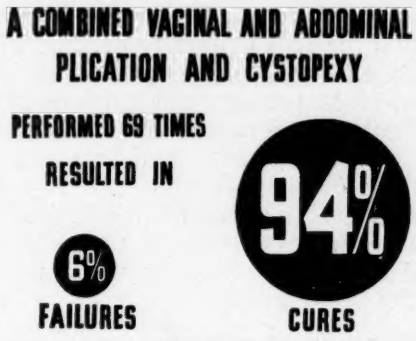


Fig. 11.

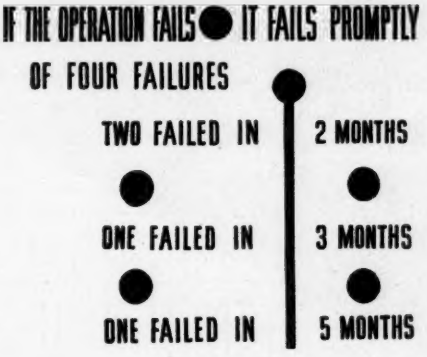


Fig. 12.

neck visualized to determine the exact degree of narrowing. We have never had to place a second tier of sutures anteriorly but this could be done where an exceptionally redundant bladder neck was found. Paired sutures are now placed along the anterolateral wall of the urethra and bladder neck and into the fibrocartilage and periosteum of the symphysis. They are most easily placed and tied in pairs from the distal end backward. As the anterolateral aspects of the urethra and bladder neck are perforated the suture is passed as a figure-of-eight for hemostasis before passing to the symphysis (Fig. 9). Three pairs of sutures usually suffice to bring the bladder neck to the junction of the middle and upper thirds of the posterior aspect of the symphysis (Fig. 10). To duplicate the normal attachments the upper sutures are successively placed farther to the side as the widening proximal urethra and bladder neck are approached. By the same token the point of insertion into the symphysis is varied according to its height and other anatomic peculiarities. The lateral recesses may be drained if slight oozing persists although it is frequently unnecessary if the tissues are gently handled and a minimum amount of swabbing

done along the lateral walls of the pelvis. The recti are approximated and the wound closed in layers. This procedure can be combined with an abdominal exploration should this be indicated.

### Results of the Operation

This operation has been performed 69 times with 94 per cent cures and 6 per cent failures (Fig. 11). The patients were tested at a six weeks postoperative check-up in the following manner. The bladder was filled with 250 c.c. of saline and the patient urged to cough hard in both the lithotomy and standing positions. A cure was listed if the patient was dry both by this test and by her own admission under other conditions of stress.

If the operation fails the fact is usually evident within a few months (Fig. 12). Three of the failures occurred among 56 cases of recurrent stress incontinence. Among a total of 13 primary applications of the procedure there was one failure after an operation in a case of congenital incontinence. In the three recurrent cases it was evident by x-ray and examination that the unfavorable result was due to failure of the plication and reposition to hold up. Two of the three had chronic bronchitis and the third was obese with a chronic cough of undetermined origin. The recurrence in the patient with congenital incontinence likewise showed a displaced bladder neck postoperatively though it was not as pronounced as the other failures.

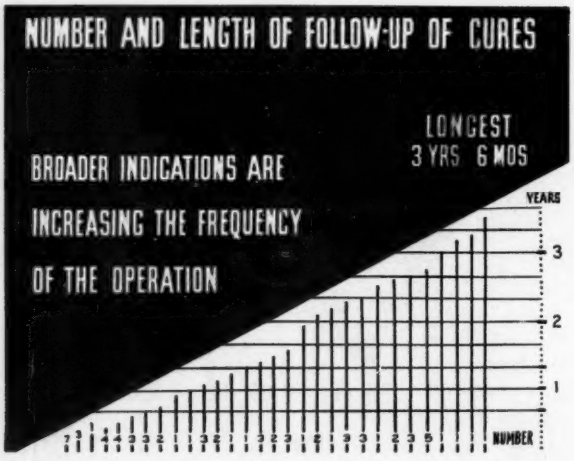


Fig. 13.

The 69 cases have been followed from a minimum of 2 months to 3 years and 6 months (Fig. 13). While the follow-up is not long, the failures have all been manifest within a few months postoperatively. This encourages us to believe that once successful the results of operation should continue to hold up.

Thirteen postoperative complications were incurred (Table I). The most common was a mild periosteitis pubis which is a relatively new entity to gynecologists as well as to urologists favoring retropubic prostatectomy. We have distinguished this mild periosteitis and chondritis with minimal or no x-ray changes from the severe syndrome of osteitis pubis originally described by Beer. Whether the disease is infectious, a posttraumatic atrophy, or due to the necrotizing effect of irritating and infected urine cannot be said. There frequently must be some leakage of urine about the sutures which may have the same effect as performing a cystotomy. Our patients showed the characteristic acute suprapubic pain and adductor spasm all out of proportion to any x-ray changes. The interpubic fibrocartilage acts like a gonorrheal joint in this respect. All were treated with intensive antibiotic therapy. More severe cases

were not seen probably due to our insistence on preoperative urinary antiseptics and a sterile urine.

Our most distressing complication occurred in a 64-year-old diabetic patient who developed a true osteomyelitis or the type of osteitis pubis with advanced x-ray changes and abscess formation. Sequestra were evident but it was not necessary to curette the bone which might have detached the bladder and made the patient incontinent again. As is commonly observed in this disease, healing did not start until the abscess was drained. A bony union at the symphysis is now replacing the interpubic fibrocartilage. Refinements in technique, especially the use of fine suture material and small-caliber needles, should reduce the complications related to bone and cartilage. Even so, the effectiveness of the operation would seem to justify the morbidity.

TABLE I. THIRTEEN POSTOPERATIVE COMPLICATIONS INCURRED

| TYPE | NUMBER |
|---|---|
| Periosteitis pubis | 5 |
| Acute ureterocystitis | 2 |
| Soft stricture of the urethra | 2 |
| Osteomyelitis of the pubis | 1 |
| Wound infection | 1 |
| Paralytic ileus | 1 |
| Thrombophlebitis | 1 |

## Conclusions

1. A composite operation including both a vaginal and an abdominal approach has been most effective in the relief of stress incontinence.

2. While the procedure is more extensive and carries with it more morbidity than the simple techniques, the results justify the added risk.

3. This operation is applicable to certain patients as a primary procedure. When marked obesity, chronic coughs, radiation bladder, and other such conditions exist, a simple vaginal plastic and plication will result in a high percentage of failures. In these patients I advocate a more extensive primary operation.

4. The space of Retzius is a logical approach to this and several other conditions of the female genital tract.

5. A mild periosteitis and chondritis of the symphysis and pubis are seen after this procedure which we have distinguished from the original Beer syndrome of osteitis pubis.

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# RECENT TRENDS IN CESAREAN SECTION AND THEIR INFLUENCE ON MATERNAL AND FETAL MORTALITY

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THE purpose of this report is to present an analysis of a portion of the data acquired from a thorough review of the obstetric activities of the Department of Obstetrics and Gynecology of The Ohio State University for the period Jan. 1, 1940, to Jan. 1, 1949. Particular emphasis has been placed on cesarean section and its results to both mother and infant. From these data, it is believed, several conclusions become self-evident. This study includes a total of 14,622 deliveries in the University Hospital and two Columbus maternity homes (equipped with hospital-type delivery services) and 2,964 home deliveries. Therefore, the total survey covers 17,586 deliveries by all methods with a total uncorrected maternal mortality of 0.157 per cent. The maternal mortality rate has steadily fallen throughout the decade and at the time of this writing there have been no maternal deaths on the service in 28 months.

A gross analysis of the over-all stillbirth and neonatal death rates as obtained from hospital totals reveals 2.8 per cent stillbirths and 2.9 per cent neonatal deaths for deliveries by all methods during this period. These are uncorrected figures and include neonatal deaths only during hospitalization. Many nonresident mothers were referred because of complications. Nevertheless, these figures compare favorably with those of the city of Columbus for the same period which show stillbirths 2.09 per cent, neonatal deaths 2.4 per cent, and maternal mortality 2.14 per cent for Columbus residents only. These same data have been collected with particular care and individually analyzed for the cases of cesarean section. All infants delivered by section and transferred to Columbus Children's Hospital have been followed to include the deaths of all such infants within the first thirty days of life.

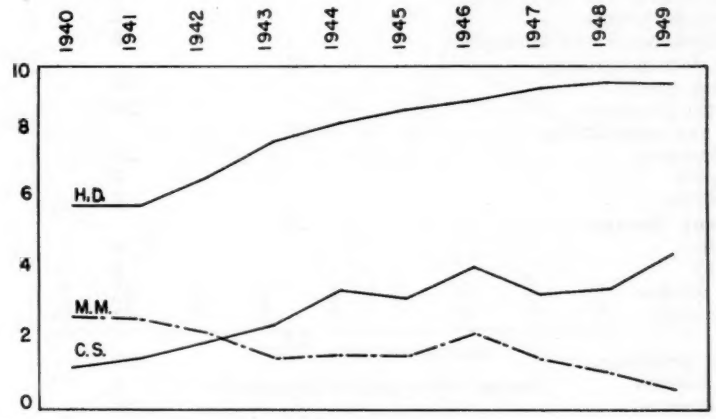
## Incidence of Cesarean Section

During the decade there have been 523 cesarean sections. This represents a section rate of 2.98 per cent for the entire service for this period. As can be seen from Table I, the rate rose during these ten years. Likewise, it is of note that the section rate has fluctuated about a relative plateau since 1944. (The 1950 rate was 3.37 per cent.) These facts seem to parallel a rather stable policy with regard to section and the criteria for it in this department since that time. This section rate certainly falls within the acceptable limits of conservatism. One postmortem section and five therapeutic interruptions of pregnancy by hysterotomy done before 28 weeks' gestation for purely maternal indications and with no effort to obtain a viable infant are not included in the

analyses. In defense of the rising section rate associated with the trend to hospitalization for parturition it need only be mentioned that a fall in maternal mortality has resulted (Fig. 1).

## Indications for Section

Classification of indications for section is made difficult by cases with multiple indications. However, the classification of related indications in groups, as used by Eastman,[1] permits the inclusion in classified orderliness of a maximum percentage of the cases with a minimum number in the miscellaneous grouping. This classification, with minor variations, has been used in Table II. Four sections done after large uterine incisions for myomectomy or hysterotomy are included with the repeat group. Cephalopelvic disproportion of all types and uterine inertia are in one subgroup because of the frequency of both indications in a given case. Nephritides include both glomerulonephritis and pyelonephritis. Two of the three cases of tuberculosis were skeletal and the disease was considered to present a mechanical as well as a medical problem. The elderly primiparas all exhibited at least one other complication which, in the absence of the state of primiparity in an older woman, would not have been a sole indication. One gravida iii with no living children is included in this group because of her age.




Trends of the Times (1940-9)
H.D.--Hospital Deliveries (%/10)
C.S.--C. section rate (%)
M.M.--Maternal mortality (%x10)

Fig. 1.

## Operative Method

The nationwide trend to laparotrachelotomy or lower uterine segment type cesarean section is reflected here. Whereas the decade 1930 to 1940 saw only 2.5 per cent low segment operations, the trend through the past decade has been steadily toward the low segment operation with transverse incision. Fig. 2 graphically illustrates this swing which resulted in an average of 49 per cent low segment operations. Seventy per cent of the sections done here in 1950 were low segment, and only 27.5 per cent classical. From Fig. 2 it can be seen that this has been a well-established trend since 1946.

From 1940 to 1950 there have been eight cesarean hysterectomies and sixteen extraperitoneal operations. The latter have not been included in the figures for the transperitoneal low flap operations.

TABLE I. INCIDENCE OF CESAREAN SECTION

| YEAR | DELIVERIES | SECTIONS* | PERCENTAGE |
|---|---|---|---|
| 1940 | 1,519 | 17 | 1.12 |
| 1941 | 1,548 | 21 | 1.36 |
| 1942 | 1,395 | 25 | 1.79 |
| 1943 | 1,408 | 32 | 2.27 |
| 1944 | 1,362 | 46 | 3.38 |
| 1945 | 1,417 | 44 | 3.11 |
| 1946 | 1,898 | 77 | 4.06 |
| 1947 | 2,295 | 74 | 3.22 |
| 1948 | 2,275 | 77 | 3.38 |
| 1949 | 2,469 | 110 | 4.46 |
| Total | 17,586 | 523 | 2.98 |

*One postmortem section and five therapeutic hysterotomies before 28 weeks' gestation are not included.

TABLE II. INDICATIONS FOR SECTION

| | | | |
|---|---|---|---|
| I. Uterine scar | 163 | | 31.2% |
| Repeat section | | 159 | |
| Myomectomy or hysterotomy | | 4 | |
| II. Mechanical dystocia | 175 | | 33.4% |
| Disproportion and/or inertia | | 148 | |
| Malpresentations | | 7 | |
| Tumor obstructing birth canal | | 8 | |
| Cervical pathology | | 3 | |
| Soft tissue scars and anomalies | | 9 | |
| III. Bleeding, late pregnancy | 91 | | 17.4% |
| Placenta previa | | 65 | |
| Abruptio placentae | | 26 | |
| IV. Toxemia and nephritides | 35 | | 6.7% |
| Pre-eclampsia | | 24 | |
| Eclampsia | | 3 | |
| Nephritides | | 8 | |
| V. Intercurrent diseases | 26 | | 5.0% |
| Diabetes | | 8 | |
| Epilepsy | | 2 | |
| Heart disease | | 13 | |
| Tuberculosis | | 3 | |
| VI. Other | 33 | | 6.3% |
| Elderly primipara | | 19 | |
| Fetal distress | | 4 | |
| Miscellaneous | | 10 | |
| | 523 | | 100.0% |

## Section Maternal Mortality

During the ten-year period there have been six maternal deaths following cesarean section, 1.14 per cent. Table III lists these cases by the year of occurrence. The one postmortem section was done in 1946 upon a patient with central respiratory failure of several hours' duration due to a ruptured congenital cerebral aneurysm and is not included. This patient had been in a state of vegetative existence in a respirator for several hours before death and the operation was done with little hope of obtaining a live baby. The six maternal deaths after cesarean section deserve careful consideration.

Of the six, three sections were done on very poor-risk patients as a last resort. The 1943 case was one of mitral stenosis with cardiac failure at rest. A section was done under local anesthesia and the 2,518 gram infant survived; the mother did not. The 1947 section was done on a patient with a dissecting aneurysm of the abdominal aorta with loss of renal blood supply resulting in complete renal failure. The infant weighed only 1,368 grams and died in the neonatal period. The 1949 case was one of severe diabetes complicated by pye-

lonephritis neither of which responded to medical management. A section was done under spinal anesthesia. The infant was of about 7 months' gestation and no preoperative evidence of fetal life was present. The infant was stillborn. The mother died in spite of this last therapeutic effort.

Of the other three, one section (1941) was performed on a patient who had preoperative pyelonephritis and who failed to deliver with 48 hours of labor because of deflection of the head. She died of her primary pyelonephritis in spite of sulfonamide medication. This patient was operated upon under general anesthesia and the 2,369 gram infant survived.

Fig. 2.

Two patients died of postoperative complications. One (1942) was sectioned for placenta previa under local anesthesia and a 3,995 gram infant survived. This mother, however, developed a postoperative small bowel obstruction caused by adhesions of a loop of ileum to a classical uterine wound and failed to survive in spite of blood transfusions, intubation, and decompression ileostomy. The other section (1945) was done after 24 hours of labor with ruptured membranes and no progress. A 3,585 gram infant survived but the mother developed a postoperative peritonitis from which she did not recover. Postmortem examination revealed a partial separation of the classical uterine wound with pyometra.

All of these deaths followed classical type operations. The first three described above were done in haste and this operative method may have been better suited for the occasion. The latter three, however, were classical sections as a matter of routine on the part of the operator and include the only deaths due solely to postoperative complications. That these complications (intestinal obstruction and general peritonitis) were directly related to the type of operation is evident. The occurrence of either complication following low segment operation would be highly improbable. From all this, then, one is

compelled to draw a single conclusion, i.e., the use of classical cesarean section should be reserved for postmortem sections. No maternal mortality has occurred here with low segment operations, either extraperitoneal or transperitoneal.

TABLE III. SECTION MATERNAL MORTALITY

| YEAR | MORTALITY | CAUSE OF DEATH AND/OR COMPLICATION |
|---|---|---|
| 1940 | 0 | |
| 1941 | 1 | Pyelonephritis—48-hour labor—sulfonamide medication |
| 1942 | 1 | Placenta previa—Postoperative intestinal obstruction |
| 1943 | 1 | Mitral stenosis—Failure at rest for 5 years |
| 1944 | 0 | |
| 1945 | 1 | Cervical dystocia—Postoperative peritonitis |
| 1946 | 0 | (One post mortem not included) |
| 1947 | 1 | Dissecting aneurysm of aorta |
| 1948 | 0 | |
| 1949 | 1 | Diabetes—pyelonephritis—pulmonary edema |
| Total | 6 | Mortality rate: 1.1% (all classical operations) |

## Stillbirths

A brief analysis of the stillborn infants delivered by section has been carried out. In this group there are 21 stillborn infants which represents a stillbirth rate of 41.1 per thousand expected live births by cesarean section. This is greater than the over-all stillbirth rate for this hospital and this community, but includes a number of infants known to be in desperate condition before operation. Table IV illustrates this point, particularly with regard to cases done for placental separation. One of the two infants included in the miscellaneous classification was also known to be dead preoperatively. That these cases, with a possible single exception, were done for purely maternal indications can be readily seen from the table. Fifty per cent of the infants were premature.

TABLE IV. STILLBIRTHS

| INDICATION FOR SECTION | | STILLBORN INFANTS |
|---|---|---|
| Bleeding, late pregnancy | | 16 |
| Abruptio placentae | 14 | |
| Placenta previa | 2 | |
| Ruptured uterus | | 1 |
| Pre-eclampsia (and fetal distress) | | 1 |
| Diabetes (and maternal distress) | | 1 |
| Miscellaneous (Indication for section unrelated to stillbirths) | | 2 |
| Total | | 21 |

No fetal heart tones present in 10 of above 14 abruptios. One in miscellaneous group known dead preoperatively.

## Anesthetic Method

In an effort to correlate it with fetal salvage, the anesthetic method has been considered. As seen from Table V, since 1946 there has been increased enthusiasm for conduction anesthesia, particularly in the form of spinal. The few cases done under caudal anesthesia are included with the spinals. Local anesthetics are listed as such.

In these cases the anesthetic method has had no apparent influence on maternal mortality. However, the correlation of anesthetic method and fetal survival is exceedingly noteworthy (Table VI). The "Rate/1,000" column in the table indicates a calculated newborn death rate on the basis of the number

of infants who died following section with a given anesthetic method. As noted, the rate for spinal is abnormally high, partly because of four exceedingly small infants. However, the exclusion of these four would result in an expected rate of 81.5 per 1,000 which is no better than that for general anesthesia. In this series the advantage has unquestionably been with those cases done primarily under local.

TABLE V. ANESTHESIA FOR SECTION

| YEAR | GENERAL | SPINAL | LOCAL | TOTAL |
|---|---|---|---|---|
| 1940 | 6 | 1 | 10 | 17 |
| 1941 | 14 | 1 | 5 | 20 |
| 1942 | 13 | 6 | 6 | 25 |
| 1943 | 13 | 5 | 14 | 32 |
| 1944 | 18 | 12 | 16 | 46 |
| 1945 | 31 | 2 | 11 | 44 |
| 1946 | 44 | 8 | 25 | 77 |
| 1947 | 34 | 27 | 13 | 74 |
| 1948 | 19 | 45 | 13 | 77 |
| 1949 | 27 | 66 | 17 | 110 |
| Total | 219 | 173 | 130 | 522 |

That the indication for section has greatly influenced these figures is realized, and therefore a careful breakdown of anesthetic method by cases has been done for the repeat sections. Inasmuch as the indication for section frequently influences the choice of anesthesia, it is logical to assume that fetal salvage results for a given anesthetic method cannot be accurately calculated. However, repeat cesarean sections should supply a fairly reliable control group, since preoperatively the type of anesthesia is purely elective. The 159 repeat sections have been so used.

TABLE VI. ANESTHESIA FOR SECTION. RELATION OF DEATHS OF NEWBORN TO EACH METHOD

| METHOD | LIVE BIRTHS | NEONATAL DEATHS | RATE/1,000 |
|---|---|---|---|
| General | 214 | 18 | 84.2 |
| Spinal | 172 | 17* | 98.9 |
| Local | 126 | 5 | 39.7 |

*Includes 2 sets of twins all of which weighed under 1,000 grams.

There were no stillbirths from repeat sections. There were 161 live births, one set of twins under spinal, and one set under local. Table VII shows the number of live births and neonatal deaths with each anesthetic method. Factors unrelated to cesarean section and anesthesia accounted for four of the eight deaths as noted. In this control group, the advantage to the infant has also been with local anesthesia. This is likely due to the minimal alteration of maternal physiology by local anesthesia.

TABLE VII. ANESTHESIA FOR REPEAT SECTION

| METHOD | LIVE BIRTHS | NEONATAL DEATHS | RATE/1,000 |
|---|---|---|---|
| General | 58 | 4* | 69.0 |
| Spinal | 60 | 3 | 50.0 |
| Local | 43 | 1† | 23.3 |

*Includes one from erythroblastosis, one anomalous infant, and one very small infant after premature labor with very small pelvis.

†Includes one erythroblastosis.

## Analysis of Neonatal Deaths

Fetal survival is affected also by other factors. First, Table VIII lists the neonatal deaths by indication for section. The expected increased risk to the

infant in placenta previa and abruptio placentae as well as in the toxemias is evident from the table. Likewise, infants from sections following abnormally long, hard labors are seen to have an increased mortality. The eight deaths following repeat sections will be further analyzed since they serve well as a control group with which to compare the factor of fetal maturity as it affects fetal salvage.

TABLE VIII. NEONATAL DEATHS

| INDICATION FOR SECTION | | NEONATAL DEATHS |
|---|---|---|
| Repeat section | | 8 |
| Cephalopelvic disproportion | | 3 |
| Bleeding, late pregnancy | | 20 |
| Abruptio placentae | 10 | |
| Placenta previa | 10 | |
| Toxemia and nephritides | | 6 |
| Preeclampsia | 4 | |
| Eclampsia | 1 | |
| Renal failure (dissecting aortic aneurysm) | 1 | |
| Other indications | | 3 |
| Heart disease | 1 | |
| Fetal distress | 1 | |
| Previous umbilical hernioplasty | 1 | |
| | | 40 |

Second, as prematurity affects fetal survival following vaginal delivery, so it does following cesarean section. The tremendous change in fetal survival after 34 weeks' gestation for infants born by section for all indications and under all anesthetics is readily apparent from the bar graph of neonatal death rate by weeks of gestation shown in Fig. 3. The 78.2 per 1,000 neonatal death rate with section is largely due to the premature group (Table IX). The cesarean section neonatal death rate among mature infants (over 2,500 grams) is seen to be only 2.4 per cent or 23.9 per 1,000 live births. Again, for comparison, the repeat section babies have been used for a control group (Table X).

TABLE IX. NEONATAL MORTALITY AFTER SECTION. ANALYSIS ACCORDING TO BIRTH WEIGHTS

| WEIGHT (GRAMS) | LIVE BIRTHS | NEONATAL DEATHS | RATE/1,000 |
|---|---|---|---|
| Under 1,000 | 11 | 11 | 1,000 |
| 1,000-1,500 | 11 | 6 | 545 |
| 1,500-2,000 | 22 | 7 | 318 |
| 2,000-2,500 | 49 | 6 | 122 |
| 2,500 and over | 419 | 10 | 23.9 |

TABLE X. NEONATAL MORTALITY AFTER REPEAT SECTION. ANALYSIS ACCORDING TO BIRTH WEIGHTS

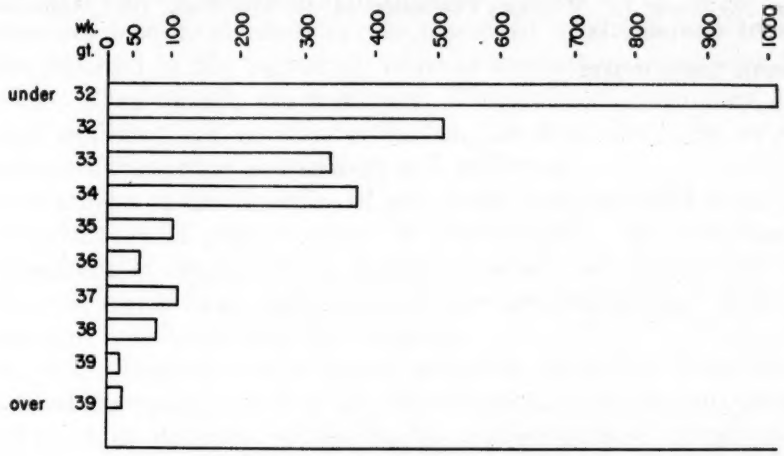
| WEIGHT (GRAMS) | LIVE BIRTHS | NEONATAL DEATHS | RATE/1,000 |
|---|---|---|---|
| Under 1,000 | 1 | 1 | 1,000 |
| 1,000-1,500 | 0 | 0 | — |
| 1,500-2,000 | 3 | 1 | 333 |
| 2,000-2,500 | 9 | 1 | 111 |
| 2,500 and over | 148 | 5* | 33.8 |

*Includes two erythroblastotic babies and one with numerous congenital anomalies. Corrected rate might read 13.5 per 1,000 live births.

Their premature rate was 8.1 per cent, evenly distributed among the anesthetic groups. The one death of an infant under 1,000 grams followed section under general anesthesia and was a case of premature labor following prior section in a woman with a very small pelvis. The death in the 1,500 to 2,000 gram group

was that of an infant born under spinal anesthesia. The two in this group who survived were delivered one each under spinal and local. Of the nine infants in the 2,000 to 2,500 gram group, four were delivered under general, three under spinal, and two under local. The one neonatal death in the 2,000 to 2,500 gram group followed general anesthesia for section. The two deaths among the term infants (2,500 grams and over) who did not have erythroblastosis or anomalies were after section under spinal.

Thus, in spite of the small number of newborn infants suitable for such an analysis, it seems quite apparent that prematurity is one of the most important contributory causes to neonatal death following section. And, although the fetal salvage by weight groups is not greatly different from that for all infants in like weight groups, the pathologic processes which lead to section frequently do so at a time when the infant is premature. The principal exception to this is repeat section and here greater care is indicated in ascertaining, in the most reliable manner, the maturity of the infant.




Neonatal deaths following section
Rate per 1000 livebirths by week of gestation.

Fig. 3.

One is led to conclude from this study that the use of conduction anesthesia, local or spinal, is to be preferred when a premature infant is expected, unless the pathology present makes such anesthesia a risk to mother or infant. And, in the case of the purely elective repeat section, the responsibility for accurate determination of fetal maturity lies with the obstetrician. In such cases a careful history and determination of the last menstruation, the date of quickening, the symptoms of lightening, and abdominal size are of great importance. X-ray estimation of fetal maturity will be of further value in confirmation of the clinical impression in these cases and might well be done routinely with great advantage.

## Summary and Conclusions

1. The lower uterine segment operation represents the safest method of cesarean section to the mother.

2. The routine use of this method will reduce the obstetrician's operating time with the low segment operation to a point where the time differential between it and the classical section will be negligible.

3. Conduction anesthesia offers the best prognosis for the infant, especially when prematurity is a factor. Local anesthesia represents the form of conduction anesthesia which alters physiology least and has the lowest neonatal death rate of any anesthetic method.

4. The stillbirth rate is not increased by cesarean section.

5. Prematurity is one of the principal causes for the neonatal death rate following cesarean section.

6. Careful, accurate determination of fetal maturity before section is of extreme importance when the time of operation can be elected.

7. In elective cases, routine x-ray determination of fetal maturity serves as a valuable aid in confirming the clinical evidence.

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# THE EFFECT ON RENAL OUTPUT OF DRUGS USED IN THE PREGNANCY TOXEMIAS*

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SINCE the toxemias of pregnancy account for the largest number of maternal deaths in the United States, and in most individual states, the ideal treatment applicable to all toxemias of pregnancy has yet to be found. However, many advances have been made in the treatment of pregnancy toxemias and have been reflected in the constantly reduced over-all maternal and fetal mortality rates. Even though the treatment of toxemia of pregnancy has undergone many modifications, no standardization has been developed as applied to the treatment of obstetric hemorrhage and infection.

The treatment of the toxemias of pregnancy has presented many parodoxes in the evolution of its present status of development. The principal features in the treatment of toxemia have always involved and emphasized the use of drugs, most of which have been employed for two indications: first, to sedate, and, second, to initiate or maintain diuresis.

Most of the scientific information available regarding these drugs represents their effects usually as they are applied to the nonpregnant patient. The few reports which do exist relative to the action of these drugs on pregnant patients have been published only recently, and refer to normally pregnant patients rather than to patients with pregnancy toxemia.

In order to gain information regarding the effect of these treatment drugs as they apply to the toxemias of pregnancy, we undertook the study to determine the effects on renal output of drugs commonly used in the treatment of pregnancy toxemia.

## Materials

Our study was carried out on 72 hospitalized patients, 63 of whom presented definite toxemia of pregnancy. The majority of the remaining 9 patients presented problems which frequently are indistinguishable clinically from the toxemias of pregnancy. All patients with toxemia of pregnancy were classified according to the classification of the American Committee on Maternal Welfare. The distribution of these cases is shown in Table I.

The basis for the final diagnosis on these patients includes antepartum, intrapartum, and postpartum observation.

## Methods

*1. Control Periods.*—While we realize that 5 per cent glucose is, in itself, a diuretic, as is inulin, we maintained in all determinations a constant rate of

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water intake by the use of a constant infusion pump. It was thus possible to introduce fluids at a constant rate of 3 c.c. per minute. Since such administration reasonably provokes criticism[1] in that glucose itself would initiate diuresis during the control period, we undertook certain measures to invalidate such criticism. By comparing time with the infusion, we used an equilibration period of 30 minutes before actually measuring the controls. After the infusion is started, there would be an immediate initiation of urinary output, at least during the equilibration period and during the first control period. Since the kidney is secreting fluid anyhow, we must determine where to begin these significant collection periods.

TABLE I

| | |
|---|---|
| Pre-eclampsia | |
| Mild | 20 |
| Severe | 30 |
| Eclampsia | 1 |
| Essential hypertension | |
| Benign | 7 |
| Malignant | 1 |
| Renal disease | |
| Chronic glomerular tubular nephritis | 3 |
| Chronic pyelonephritis | 1 |
| Others | |
| Edema without toxemia | 2 |
| Raynaud's disease | 1 |
| Cirrhosis of the liver | 1 |
| Postoperative nephrectomy | 2 |
| Mitral stenosis with failure | 1 |
| Normal ante partum | 1 |
| Normal post partum | 1 |
| Total | 72 |

As noted in Fig. 1, where each bar represents three periods for a single patient, we show that each patient was studied with reference to a comparison of the last three control periods with the first three control periods. Each patient was studied over six control periods. This would seem to obviate the explanation that the effect of any drug given might be eclipsed by water diuresis.

In order to demonstrate the effectiveness of such an increase in the number of periods used in the control, it will be seen that, when we compare the last three control periods with the first three, a smaller urinary output in the first three would result because of the graduated rise in the urinary output during these periods. Thus, the actual output of the first three periods represents a geometric summation. We would thus expect from such a summation, a greater amount of urinary output in the last three control periods than during the first three periods. This is shown to be so in our 54 patients so evaluated. It thus becomes apparent that the over-all average of urinary output for these six periods of control is mathematically acceptable.

During our total study, which requires approximately five hours per patient, two intravenous infusions are running. Into one antecubital vein, inulin and para-aminohippuric acid are injected, while into the other vein is injected 5 per cent glucose in distilled water in order to keep a "vein open," since blood is drawn every 20 minutes for the simultaneous determination of renal clearance.

*2. Test Periods.*—After preliminary equilibration and control periods, patients were tested with drugs commonly used in the treatment of toxemia of pregnancy. These drugs were administered in the same manner as used in the treatment of the condition. Renal output was measured in the same manner

as during the control periods, and the bladder completely emptied at the end of each period, both control and test. In order to ensure complete collection of all of the urinary output for a given period, the bladder was washed with each collection.

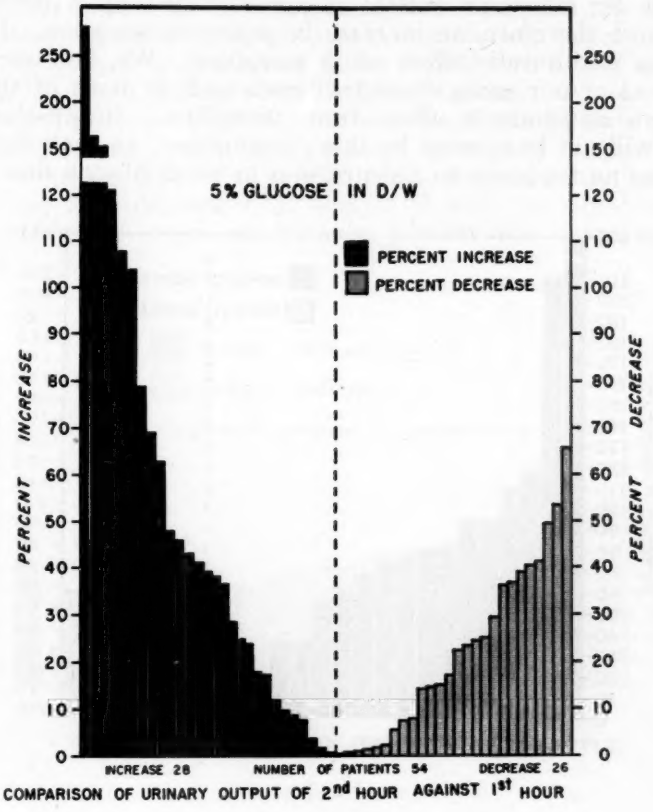



Fig. 1.

## Morphine

Since morphine is a very commonly used drug in the treatment of pregnancy toxemia, we evaluated its effects more thoroughly than those of any of the other drugs studied. The drug was administered in the form of morphine sulfate in 16 mg. doses hypodermically to 25 patients with toxemia of pregnancy. As has been previously noted, the drug was administered after six control periods, in ten patients, and these were followed through six test periods following the administration of the drug. To the other 15 patients, morphine was given following three control periods and its effects evaluated through three test periods.

As noted in Fig. 2, of our 25 patients who were given morphine, seven, or 28 per cent, showed a decrease in urinary output. Of these seven patients showing a decrease in urinary output following the administration of morphine, none showed any really significantly marked decrease except one patient who showed a decrease of 58.5 per cent.

Eighteen patients who received morphine showed an increase in the urinary output. This increase ranged from a 10.8 per cent increase at the one extreme, to an increase of 833 per cent at the other extreme over the control average.

Considering the entire group, we find the increase to average 115.6 per cent above the control average. Such relationships make it obvious that, at least in patients with pregnancy toxemia, morphine acts in a distinctly diuretic manner.

Bradbury and Brown and associates[3, 4, 5, 6] have stated that the mechanism of antidiuresis by morphine sulfate is accomplished by a decrease in renal plasma flow, and, therefore, an increase in water reabsorption. De Bodo[7] likewise reports an antidiuretic effect using morphine. We, however, demonstrate that 72 per cent of our cases showed diuresis and, in none of these, could we demonstrate an antidiuretic effect from morphine. In another publication whose details will not be covered by this presentation, we shall show that, in all cases, there was no tendency to a depression in renal plasma flow by morphine.

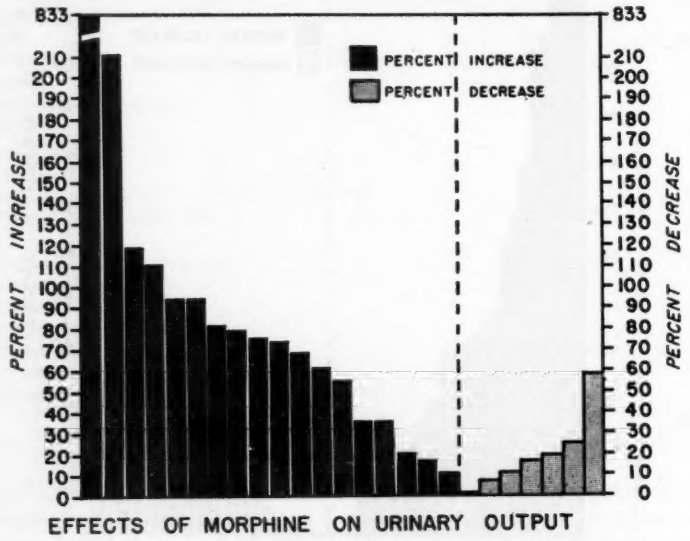



Fig. 2.

In this morphine series, the urinary output and oral intake in five patients were accurately measured for twelve hours following the completion of the previously described five-hour tests. When we compare the urinary output with the oral intake of fluid in these five patients, the actually measured urinary output was found to be less than the intake in all patients. This is as it should be since the urinary output is not expected to represent an exact excretion of introduced fluid. All patients retaining their oral fluid had good diuresis averaging 4 c.c. of urine per minute during the twelve-hour period. It should thus be apparent that morphine exerted relatively little if any antidiuretic effect in this twelve-hour period.

## Meperidine (Isonipecaine)

Practically nothing has been reported regarding the pharmacologic action of meperidine on renal function. Even though its use has increased sharply in recent years and since the drug is used in significantly large doses, no clarification of its renal implications has been exhaustively presented. The drug is stated[2] to act on smooth muscle in general by producing relaxation; in addition, it possesses the properties of producing relaxation of ureteral and bladder musculature as well. Because meperidine has actually assumed a place of being an almost universal substitute for morphine by virtue of its relaxation effects,

we have endeavored to determine whether its renal effects parallel those of morphine in pregnancy toxemia. Ferrer and Sokoloff[8] have suggested an antidiuretic effect with the use of Demerol in congestive heart failure.

Meperidine, in 100 mg. doses, given hypodermically, was administered to 25 patients in our study, 24 of whom had toxemias, and one of whom was normally pregnant. Each of these patients, immediately prior to the administration of the drug, had been studied under equilibration and test periods as previously noted. Eight patients were studied through six test periods after an equal number of periods of control. It was found among these eight patients that seven (87.5 per cent) revealed a decrease in urinary output following the administration of meperidine. The rate of renal output during these test periods averaged a 51 per cent depression as compared with the renal output during the control periods. In only one toxemia patient was there an increase in urinary output.

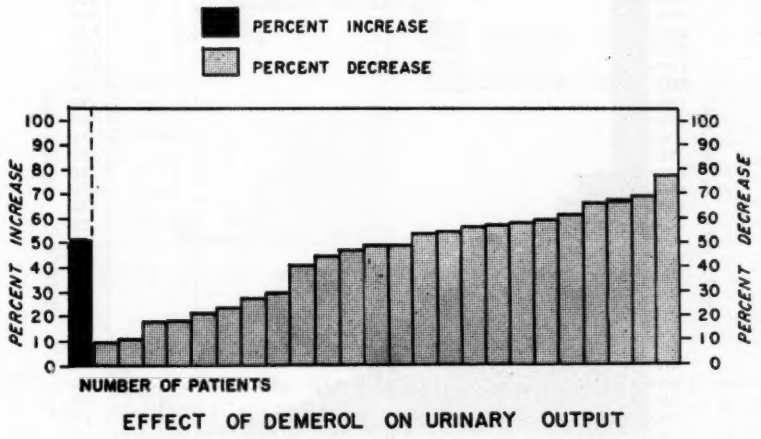



Fig. 3.

Among the other 17 patients to whom meperidine was given, the drug was administered with other drugs with a carefully measured output and intake and evaluation of each period. Thirteen of these patients received a combination of ¼ grain of morphine, followed by a standard dose of aminophylline (1.25 mg. per square meter of body surface) and these drugs were followed by the standard dose of meperidine. In these patients, a pronounced depression in the urinary output was observed in all but one case following the administration of meperidine. In noting the general trend of events, morphine produced a diuresis of a moderate degree, aminophylline further exaggerated the diuresis, but meperidine evoked a tremendous drop in renal output. In combining the patients who received meperidine alone and those who received meperidine in combination with other drugs, we note in Fig. 3 that a decrease in urinary output is apparent in 24 out of the 25 cases studied.

Where meperidine alone was the test drug, glomerular filtration rates and renal plasma flow determinations were made on three patients. Each of these patients revealed a decrease in the renal plasma flow, and in two of the three patients, the glomerular filtration rate was decreased. Among those to whom meperidine was given in combination with other drugs, the renal plasma flow after the administration of meperidine was decreased in 13 of the 16 patients studied.

## Aminophylline

Aminophylline was administered to 31 of our patients as the test drug. One of these patients had cirrhosis of the liver, while another presented only massive edema associated with the pregnancy. While most descriptions relative to the effects of aminophylline have been recorded in reference to the nonpregnant patient, Brown and Bradbury have studied its effect in the normal pregnant patient. They found that when small doses were given (0.13 to 1.5 Gm. per day) there was no effect. However, with the administration of large doses, they noted an increase in sodium loss and an increased urinary excretion as well. Vomiting was a common complication following the administration of the drug.

Aminophylline was used as the only test drug in 16 of our patients, and was given in combination with other drugs to another 15 patients (Fig. 4).

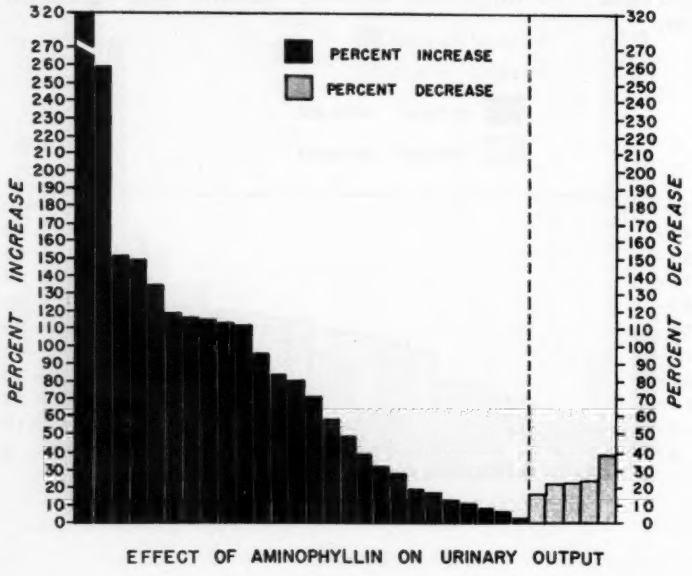



Fig. 4.

Aminophylline is a xanthine drug containing 70 per cent theophylline in conjunction with ethylenediamine. This is the xanthine preparation usually given by parenteral administration. It is the most potent of the xanthine diuretics.

When aminophylline was used alone, we found it to be diuretic in 14 of the 16 patients. In determining the average increase in urinary output, we found it to be 94.5 per cent over the control average with the increase in urinary output ranging from a low of 18.9 per cent to a high of 152.8 per cent over the control periods. Where morphine was used in conjunction with aminophylline (15 cases), diuresis resulted in 12 of the 15 determinations.

Glomerular filtration rates and renal plasma flow were determined 29 times among this group of patients receiving aminophylline. In practically all instances, not only was the renal plasma flow increased but so was glomerular filtration rate increased. This would seem to indicate that aminophylline induces a significant increase in renal plasma flow, at least in pregnancy toxemia, and thus accounts for the diuretic effect of the drug in these patients.

## Magnesium Sulfate

Magnesium sulfate, one of the very commonly used drugs in the treatment of pregnancy toxemia, is absorbed from the gastrointestinal tract with difficulty.

Its use by mouth is designed principally to produce catharsis and the elimination of body water through the gastrointestinal tract. Thus, its principal use in the toxemias of pregnancy is by intravenous or intramuscular administration in order to effect its properties of sedation and central nervous system depression, particularly to control convulsions. After intravenous administration, magnesium sulfate is effective for only approximately 30 minutes. Its main action produces not only depression of the central nervous system, but a depression of the peripheral neuromuscular apparatus as well.

Since magnesium sulfate, as a treatment of toxemia of pregnancy, is never the only drug used to control the toxemia, it does not seem plausible to apply all the good results obtained in the treatment of toxemia of pregnancy to this single drug. It is usually given in combination with fluids, which in themselves will promote a diuresis, and practically always is given in conjunction with morphine sulfate which, as we have shown, is diuretic.

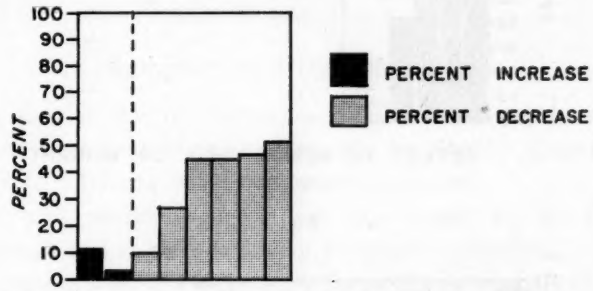



Fig. 5.

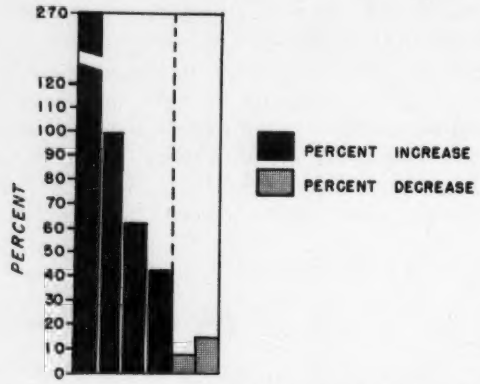
Following control periods, magnesium sulfate was administered intravenously to eight of our patients in our standard dose of 2 c.c. of a 50 per cent solution, which is one-half the usual therapeutic dose. Of our 8 patients (Fig. 5), six showed a depression of renal output amounting to an average of 38.1 per cent less than the control average. The reduction in output varied from a low of 10.6 per cent to the greatest depression of 53 per cent. It will be noted that of the two patients showing diuresis following magnesium sulfate, the average increase in urinary output was only 7.91 per cent over the control average.

Our patients were given relatively small doses of magnesium sulfate, and, clinically, showed very little effect from the drug, either in the form of drowsiness, syncope, vasomotor collapse, or depression of reflexes. In view of the depression of urinary output in 75 per cent of our cases, as a result of the relatively small dose employed, one can only wonder what must happen to renal excretion when larger doses are used over repeated intervals as employed on many obstetrical services for the preconvulsive and convulsive types of toxemia of pregnancy.

## Mercuhydrin

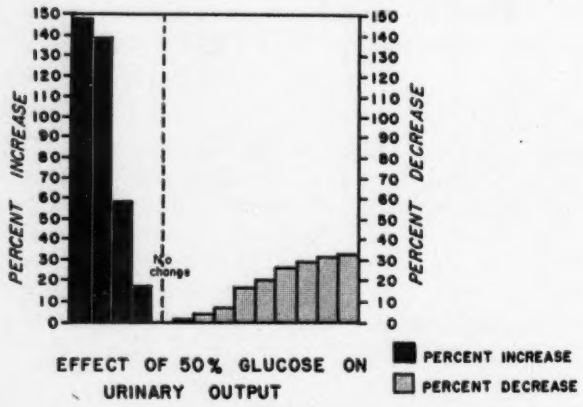
Since mercurial diuretics are commonly used in edema of cardiac and nephritic origin, considerable speculation arises as regards their effect in pregnancy toxemia. Because the mercurials act on the renal tubules by provoking a very early stage of toxicity in the kidney, we have been reluctant to use mercurials on relatively normal kidneys. We believe this to be so because the kidneys in the majority of true pregnancy toxemias, as noted on late postpartum evaluation of the kidney, reveal no evidence of residual renal damage from the toxemia. We feel that the use of such a preparation on a normal kidney would

provoke damage that was not already there. On the other hand, where extensive renal damage is present, we would prefer not to enhance any such damage by the use of mercurial preparations. The use of mercurial diuretics, in our experience, has revealed them to be the most powerful sodium diuretics of any of the preparations used by us in our study and treatment of pregnancy toxemia.




EFFECT OF MERCUHYDRIN ON URINARY OUTPUT

Fig. 6.




EFFECT OF 50% GLUCOSE ON URINARY OUTPUT

Fig. 7.

Mercuhydrin was employed in six patients (Fig. 6). Five of these patients received the drug alone while the sixth patient was given the drug following the administration of glucose and meperidine. The urinary output was increased in four of the six patients with an average of 119.3 per cent increase in renal excretion over the control average.

The glomerular filtration rates and renal plasma flows were determined in these six patients. Four of our patients showed an increase in both the glomerular filtration rate and renal plasma flow.

## Glucose

Probably the most commonly used drug in the management of pregnancy toxemia is hypertonic glucose. Glucose is characteristically administered, in most clinics, in hypertonic solutions with the aim of reducing edema, particularly

of the cerebral type. The usual dosage given is 50 c.c. of a 50 per cent solution intravenously. Since most glucose must be metabolized in the liver and deposited in the liver as glycogen, it seems that its edema-reducing potentialities have been generally overrated. It would also seem that most of these beliefs are based upon impression rather than actual investigation. In our experience, isotonic solutions of glucose have been considerably more effective in promoting diuresis than have hypertonic solutions.

Theoretically, the glucose which escapes reabsorption in the proximal tubule of the kidney should then exert an osmotic effect in the loop of Henle, and thus bring about excretion of water. Thus, in our use of 50 c.c. of a 50 per cent solution of glucose, we should theoretically have produced diuresis in the majority of our patients. As noted in Fig. 7, we failed to produce diuresis with this drug. It will be seen that, among our 14 patients to whom 50 per cent glucose was administered, nine showed a decrease in urinary output, with the decrease average being 19.1 per cent below the control average. This decrease was represented among 64.3 per cent of all our patients.

## Summary and Conclusions

1. We believe that it can be shown, on the basis of our investigation, that morphine, aminophylline, and Mercuhydrin can be clearly classified as diuretic when administered to patients with pregnancy toxemia.

2. Meperidine and magnesium sulfate are found to be distinctly antidiuretic when administered to patients with pregnancy toxemia.

3. Statistical analysis of the effects of these drugs reveals the effects to be significant.

4. Statistical analysis of the effects of 50 per cent glucose supports neither a diuretic nor an antidiuretic effect. We would conclude, then, that 50 per cent glucose supplies only fluid and calories.

5. The effect on renal plasma flow depends on the drug used and upon the type of toxemia present in the patient to whom the drug is administered.

6. Our studies would indicate the continuation of this investigation by other observers.

We wish to acknowledge with thanks the generosity of Mr. R. J. Coleman of the U. S. Standard Products Co., of Woodworth, Wis., in supplying us with the inulin used in this study.

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# CAUSES AND PREVENTION OF DEFECTIVE HEMOSTASIS, TOGETHER WITH A TECHNIQUE FOR TOTAL HYSTERECTOMY

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THE question of dissecting a narrow bridge of tissue such as the parametrium, where more than one ligature is required to achieve hemostasis, poses a number of interesting technical problems.

The commonly used clamps which are replaced by ligatures have many disadvantages. Frequently, these clamps do not close properly, with the result that some tissue is allowed to escape either at the point of the instrument or at its hinge. Furthermore, the clamps tend to crush the tissue, and crushed tissue is more likely to retract from the ligature loop. This cannot always be prevented by tying the ligature from the center of the stump to both sides, or by using modified mattress or figure-of-eight sutures; nor can the problem be solved by cutting around the tip of the clamp, as is frequently done with the object of forming a more serviceable neck. Another disadvantage inherent in the common clamps is that they must be opened in order to tighten the replacing ligatures. If one of these ligatures tears, bleeding will result; and there is often considerable danger involved in the matter of catching a retracted artery, for example, in the neighborhood of the ureter. It is unquestionably much safer to tie the ligature first, and then to cut. Widespread recognition of this fact is the reason why many surgeons frequently refrain from using clamps and apply only simple suture-ligatures or ligatures on carriers, but the fact remains that, regardless of whether one uses clamps replaced by ligatures or only ligatures on needles or carriers, hemorrhages still constitute a common complication. A search for the causes of defective hemostasis has revealed that a hidden technical error is responsible in most instances of slipping ligatures and escaping stumps; and it is very interesting to note that the same error is the cause of many a hemorrhage, even in cases where the ligatures do not slip and the stumps do not escape from the ligature loops.

It may be illustrated on two consecutive stumps (Fig. 1). The first suture ligature is applied and tied around the margin *(m)* of the bridge of tissue, which should be dissected. An equilateral, conical stump *(st 1)* is readily formed, and the separating cut *(sc)* is made. The next suture ligature *(L)* should be properly tied around *b*. Instead, however, the ligature is all too commonly tied around a point, which is more or less distant from *b*. The following separating cut leads to the formation of a short, tapering stump *(st 2)*, and that is the most dangerous shape for a stump to have. The ligature loop *(1)* which slips along the edge of such a stump gets loose. The tissue, either all or in part, can readily escape and the danger of hemorrhage is obvious.

Even in cases where the second ligature does not slip and the tissue does not escape from the ligature loops, this technique leaves an area *(A)* between the ties, which is not ligated. Bleeding will result, because the ligatures have not been placed close enough to each other; and this, in turn, is due to the fact that there is no pathway through the tissue to bring the second ligature in close proximity to the first one.

To overcome this difficulty, I have suggested making an incision between the line of separation (*sc*) and the first ligature (Fig. 1, *4*) in order to open the way for the second tie. This incision *(tc)* is termed the transverse cut, for the simple reason that it is transverse to the line of separation. This transverse cut makes it possible to tie the second ligature not only properly around *b* and to form a reliable, equilateral, conical stump *(st)* but also to place the second ligature close to the first one. It is absolutely essential for the transverse cut, to go the entire distance from the line of separation to *b*, in other words, to reach the ligature itself. A mere "nick" around the stump is not enough, because an area which cannot be encircled with the second ligature would cause a bleeding from the first stump (Fig. 1, *2*). Oozing of the first stump will naturally suggest that its ligature is not properly tied. However, the most frequent, real reason for such oozing is that the second ligature has not been placed close enough to the first one, because no transverse cut was done *(1)* or the transverse cut was too short *(2)*. If the transverse cut *(tc)* has been correctly performed but the second ligature *(L 2)* has not been placed close enough to the previous one (Fig. 1, *3*), again an unligated area *(U)* will remain, and the result will be a bleeding between the ligatures.

| Cause | Site | Prevention | Wrong Correct |
|---|---|---|---|
| Incorrect location of second ligature (L)<br>Stump (st-2) becomes tapering<br>Ligature (L) slips and loop (l) gets loose<br>Tissue (T) retracts<br>Area (A) not ligated | Stump 1<br>Stump 2 | Transverse cut (tc) | |
| Transverse cut (tc) is too short | Stump 1 | Extension of transverse cut (tc) all the way from separating cut (sc) to the ligature (L) | |
| Extent of transverse cut (tc) is correct but 2nd ligature (L-2) is not placed close enough to 1st one (L-1) | Between ligatures (L-1) & (L-2) | Placing the ligatures (L-1) and (L-2) very close to each other | |

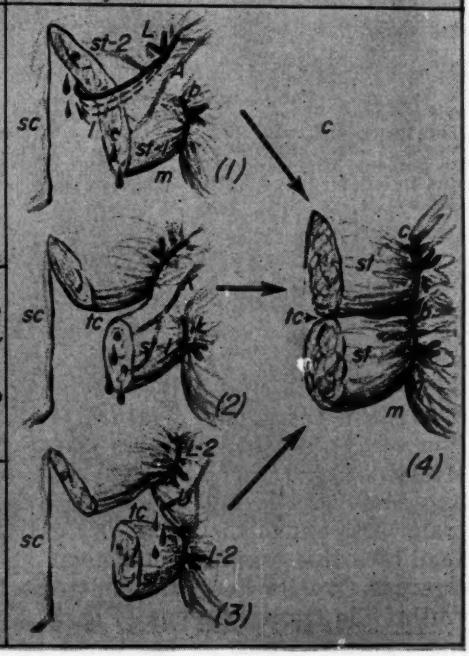


Fig. 1.—Cause, site, and prevention of defective hemostasis.

As a practical consequence of these investigations, I developed a new technique for the separation of a bridge of tissue, called the Cylinder Clamp Technique (CCT), because the new clamp which I designed for this purpose

carries a hollow cylinder *(CC)* at the tip of the blades (Fig. 2). This new device offers many advantages: (1) The tissue *(T)* which will form the stump, is embraced by this clamp and not crushed. (2) The applied ligature *(L)* can be tightened while the cylinder clamp *(CC)* remains in place, because the encircled tissue in the cavity of the cylinder readily yields to the traction of the ligature loop *(L)*. (3) The embraced tissue is ligated before it is cut; thus, if a tie is broken, it can be replaced without incurring the risk of a hemorrhage. (4) The closure line of the blades *(cl)* is of outstanding importance to the entire technique. Its lateral end *(L)* is the point where the suture ligature is to be placed. The central end *(C)* of the closure line marks the termination of the separating cut. The closure line itself *(L to C)* shows the location and extent of the transverse cut.

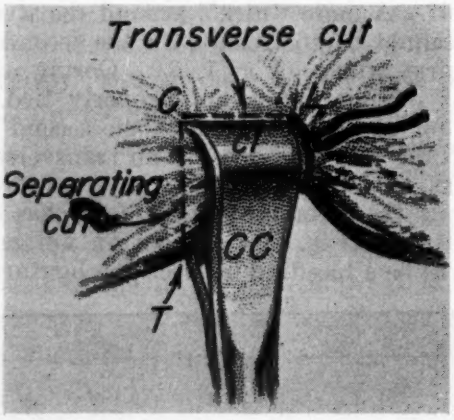


Fig. 2.—The cylinder clamp. The tissue (*T*) which will form the stump is embraced and not crushed. The ligature (*L*) is tightened while the cylinder clamp (*CC*) remains in place. The tissue is ligated before it is cut. The closure line (*cl*) of the blades is an important landmark of the technique. Its lateral end (*L*) indicates the point where the ligature (*L*) should be placed. The central end (*C*) indicates the termination of the separating cut. The closure line itself, from *L* to *C*, shows the extent of the transverse cut.

## The Cylinder Clamp Technique (CCT)

The first cylinder clamp *(C)* encircles the available margin *(M)* of a bridge of tissue (Fig. 3, *A*). The ligature *(L)* is placed (Fig. 3, *B*) and tied, the separating cut is performed and then the transverse cut *(T)* is done. (Fig. 3, *C*.) The second cylinder clamp *(C 2)* encircles the next tissue area (Fig. 3, *D*) and the second ligature *(L 2)* is placed at the lateral end of the closure line of the second cylinder clamp *(C 2)* (Fig. 3, *D*). And now it must be stressed that the following step is of the greatest importance. As previously explained, the second ligature *(L 2)* (Fig. 3, *D*) must be carried through the transverse cut to the point *(E)* extremely close to the first ligature. In order to facilitate this essential maneuver and secure the proper location of the second ligature *(L 2)* a long and fine hemostat *(G)* is applied at *E*, which is the lateral end of the transverse cut (Fig. 3, *E*). The hemostat serves only as a guide for the ligature which is tightened laterally to this so-called ligature guide *(G)* (Fig. 3, *F*). The same ligature *(L 2)* is now used to retie the first stump (Fig. 4) (retying maneuver). This is readily accomplished, because the first cylinder clamp has remained in place. The separating cut is then extended and the second transverse cut is performed from the second ligature to the central end of the second cylinder clamp in the same way as shown in Fig. 3, *C*. The

first cylinder clamp is then removed and used to encircle the next area of the tissue bridge. This climbing maneuver with the cylinder clamps may be repeated as many times as necessary.

The cylinder clamp technique may be advantageously used in any case where a bridge of tissue is to be dissected, and is particularly helpful in

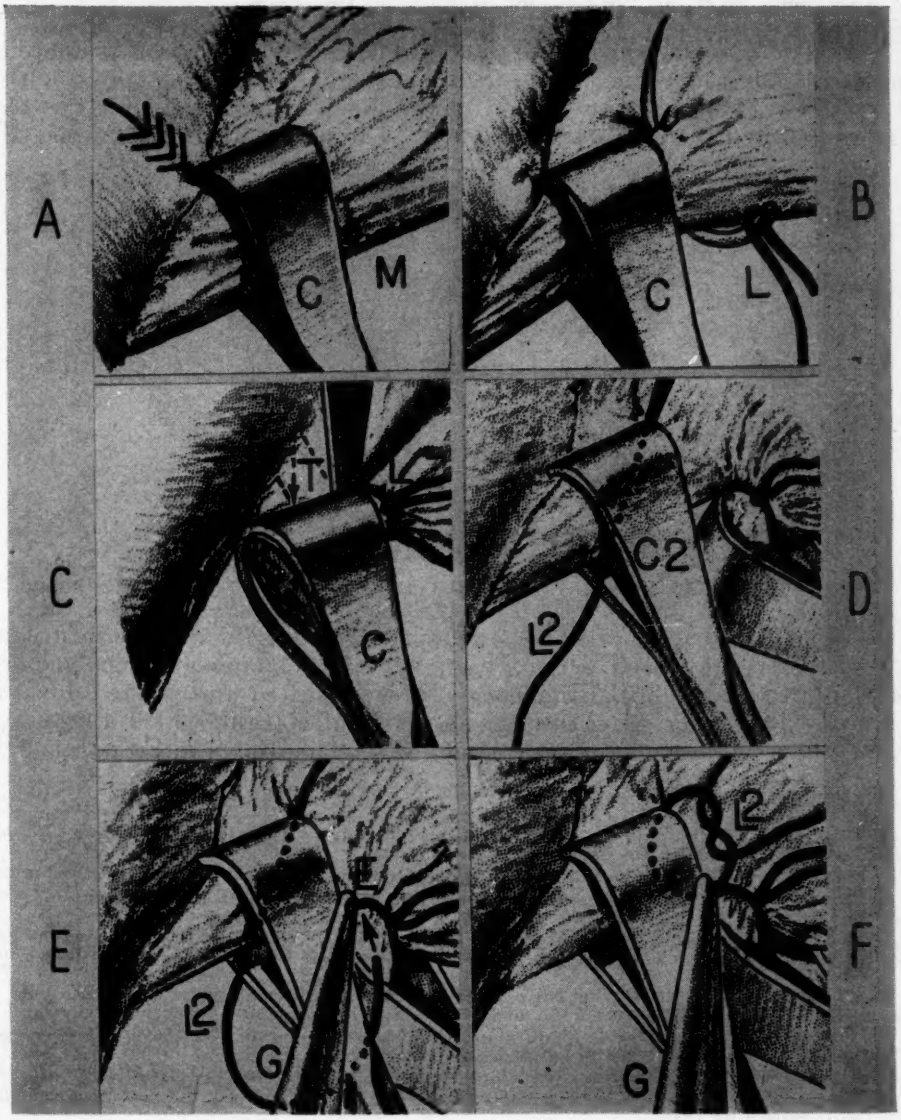


Fig. 3.—

*A*, The first cylinder clamp (*C*) encircles the margin (*M*) of the bridge of tissue. The instrument forms with the margin (*M*) an angle of 90 degrees.

*B*, The suture ligature (*L*) is placed at the lateral end of the closure line of the cylinder clamp (*C*).

*C*, The ligature (*L*) has been tied and the separating cut (*S*) performed. The transverse cut (*T*) is made along the closure line of the blades.

*D*, The second cylinder clamp (*C 2*) has been applied. The second ligature (*L 2*) is placed at the lateral end of the closure line of the instrument (*C 2*).

*E*, The ligature guide (*G*) is applied at *E* which is the lateral end of the transverse cut. The ligature (*L 2*) is carried through the transverse cut to the point (*E*).

*F*, The ligature (*L 2*) is tightened lateral to the ligature guide (*G*) in order to place the ligature (*L 2*) very close to the first one.

cases where this bridge is narrow and vascular. The parametrium, which contains the large uterine vessels and many smaller branches, offers only a limited area for the formation of stumps, because of the proximity of the ureter. Total hysterectomy is therefore an operation for which the cylinder clamp technique is most useful.

### The Cylinder Clamp Technique for Total Hysterectomy

The abdomen is opened, and the bladder with the ureters is thoroughly separated from the cervix. The cylinder clamp technique starts with the first cylinder clamp at the left infundibulopelvic ligament and the second cylinder clamp at the left round ligament. The suture ligatures are placed and

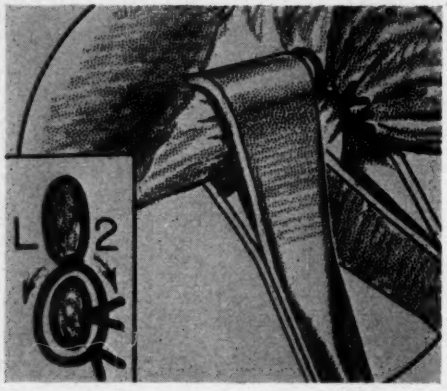


Fig. 4.—Retying maneuver. The ligature (*L 2*) is used to retie the first stump.

the cuts performed in the manner as described above. After the infundibulopelvic ligament has been retied, both cylinder clamps are removed. The avascular area of the broad ligament is now dissected and pushed downward and to the side. This move creates an artificial margin, which allows a new start of the cylinder clamp technique for the ligation of the parametrium.

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Fig. 5.—The ligation of the parametrium.

*A*, The cylinder clamp (*CC*) is applied perpendicular to the artificial margin (*M*) of the *left* parametrium, including the left uterine artery.

*B*, The needle is placed at the lateral end of the closure line (*cl*) of the cylinder clamp.

*C*, The ligature (*L*) is tied around the margin (*M*) of the left parametrium. No cut is done.

*D*, The cylinder clamp (*CC*) has been applied to the *right* parametrium including the right uterine artery. The ligature (*L*) has been placed and tied around the artificial margin (*M*) of the parametrium.

*E*, The separating cut (*sc*), which also severs the right uterine vessels, is made very close to the uterus (*U*) up to the level of the closure line (*cl*) of the clamp. No reflux clamp is used.

*F*, The transverse cut (*tc*) is made along the closure line from the ligature to the separating cut by stablike motions with a pointed knife.

*G*, The next portion of the parametrium is embraced with another cylinder clamp (*C 2*).

*H*, The needle (*N*) which carries the ligature (*L 2*) has pierced the tissue at the lateral end of the closure line (*cl*).

*I*, The ligature guide (*G*) has been applied at (*E*) which is the lateral end of the transverse cut. The ligature is carried under the second cylinder clamp and the ligature guide (*G*).

*J*, The ligature (*L 2*) is tied laterally to the ligature guide (*G*) close to the previous ligature.

*K*, The ligature guide has been removed. The last ligature (*L 2*) is used to retie the previous stump. Retying maneuver (insert).

*L*, The first cylinder clamp has been removed; the separating cut has been performed; the transverse cut (*T*) is made.

*M*, The next portion of the parametrium has been encircled with the cylinder clamp. The ligature has been applied and tied. The second cylinder clamp has been removed. The separating cut is extended. The vagina (*V*) is opened laterally.

*N*, (*E* to *M* has been repeated on the left side. The uterus has then been removed.) A separate mattress suture (*A*) which includes the angle of the vagina is placed around the closure line of the last cylinder clamp, on the left parametrium.

*O*, A separate mattress suture (*B*) is placed around the closure line of the cylinder clamp which has been left on the last portion of the right parametrium.

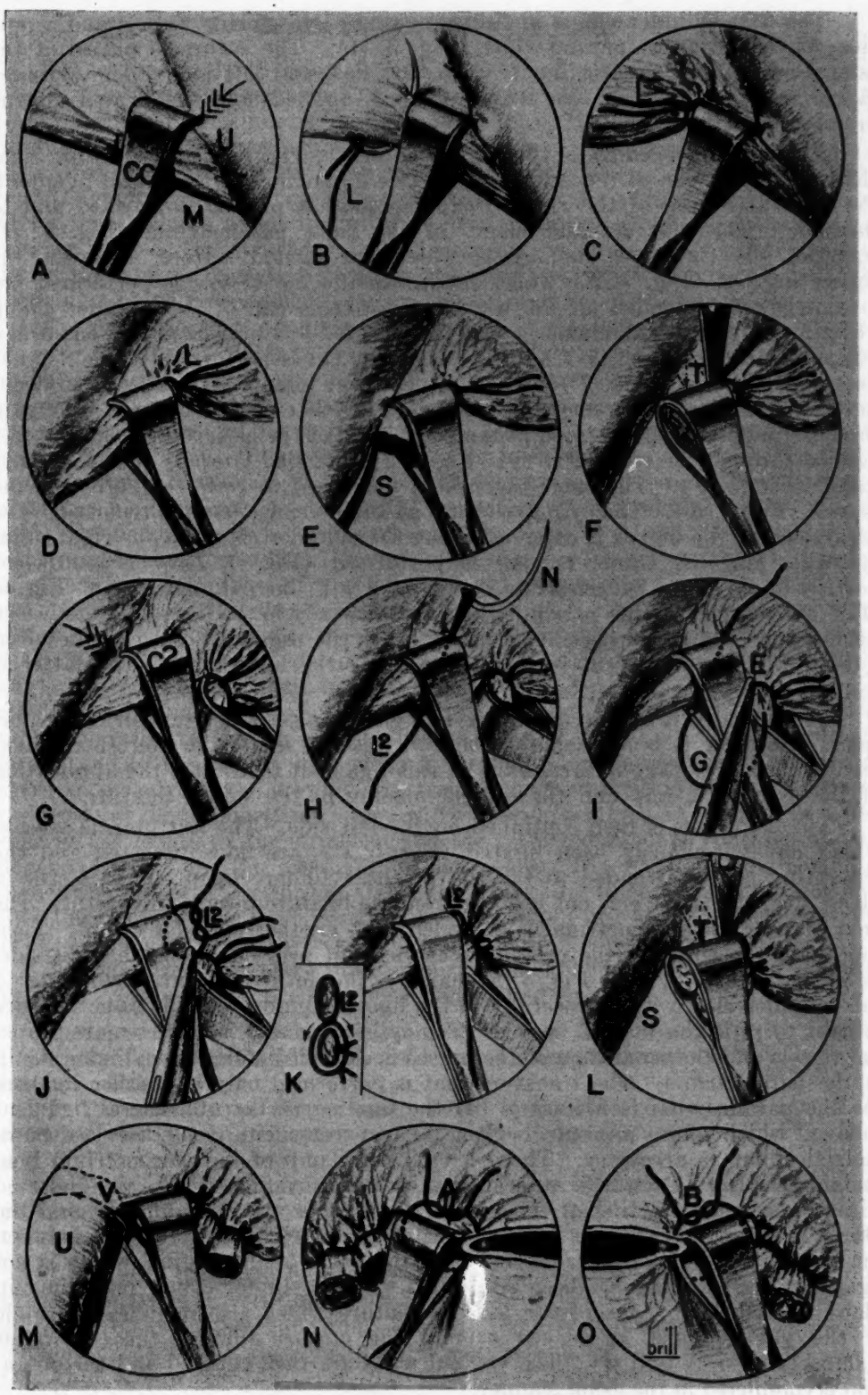


**Fig. 5.**—*For legend see opposite page.*

The first cylinder clamp encircles now the left uterine vessels and a portion of the adjacent parametrium (Fig. 5, *A*). The suture is placed at the lateral end of the closure line (Fig. 5, *B*), tied, and left long. The cylinder clamp remains in place. No reflux clamp is applied, and the ligated uterine vessels are not cut (Fig. 5, *C*).

The whole procedure is then repeated on the right side. Following ligation and separation of the infundibulopelvic ligament and the round ligament, the avascular area of the right broad ligament is pushed downward and to the side. The first cylinder clamp of the right parametrium (Fig. 5, *D*) encircles the right uterine vessels which are ligated. Here, however, the separating cut (Fig. 5, *E*) which severs the uterine vessels is performed immediately and extended all the way to the uterine end of the cylinder clamp (Fig. 5, *E*). No reflux clamp is used, because the left uterine artery has previously been ligated (Fig. 5, *C*). The transverse cut is performed in the manner described above (Fig. 5, *F*). The next cylinder clamp encircles the adjacent portion of the right parametrium (Fig. 5, *G*). The suture ligature belonging to the cylinder clamp is placed at the lateral end of the closure line (Fig. 5, *H*), carried through the transverse cut (Fig. 5, *I*), and tied laterally to the ligature guide (Fig. 5, *J*). The same ligature is now used to retie the right uterine vessels (Fig. 5, *K*). The cylinder clamp on the uterine vessels is removed. The separation of the uterus is extended along the cylinder clamp at the right parametrium, and the transverse cut is performed (Fig. 5, *L*). The adjacent portion of the right parametrium is encircled with the cylinder clamp (Fig. 5, *M*). The suture ligature is applied and tied laterally to the ligature guide. The extension of the separating cut generally opens the vagina *(V)* at the side (Fig. 5, *M*). No transverse cut is performed along the last clamp. The latter is to remain in place.

Occasionally it is not necessary to ligate the parametrium in three portions. However it is advisable, in many a case, to ligate the uterosacral ligament separately. The natural edge of this ligament facilitates the application of the cylinder clamp and the correct placing of the suture ligature.

The operation is then continued on the left side. The left uterine vessels, which have previously been ligated (Fig. 5, *C*), are now dissected and the separating cut is extended to the end of the cylinder clamp which is still in place; then the transverse cut is made from the ligature toward the uterus. The next area of the parametrium is encircled with another cylinder clamp. Then there is a repetition of the procedure carried out previously on the right side, as shown in Fig. 5, *I*, to Fig. 5, *M*, namely, the suture ligature belonging to this cylinder clamp is tied laterally to the ligature guide, and the same ligature is used to retie the uterine vessels. The cylinder clamp is then removed from the vessels and the separation of the uterus is extended along the cylinder clamp at the parametrium. The transverse cut is performed only if another ligature for the parametrium is necessary. If the ligation of the uterosacral ligament follows, which offers a natural edge, no transverse cut along the last parametrial stump is necessary. The last cylinder clamp of the parametrium is to remain in place. Now the anterior and posterior vaginal walls are dissected with the scissors, starting at the hole in the vagina at the right side, and the uterus is removed. There is an area, located on the right and left sides between the last ligature of the parametrium and the angle of the vagina, which is not ligated. The bleeding has been controlled by the cylinder clamp remaining in place on each side. A separate mattress suture which also includes the angle of the vagina must be placed around the closure line of these cylinder clamps (Fig. 5, *N* and *O*). The vaginal walls are then sutured and the operation is completed in the usual manner.

## Comments and Technical Hints

The cylinder clamp must always be applied with particular care; once closed, a cylinder clamp should not be opened and reapplied. The cylinder clamp for the infundibulopelvic ligament, if the adnexa are to be removed, or for the tube and ovarian ligament, if the adnexa are to remain, should encircle the entire area of tissue up to the round ligament. The cylinder clamp for the round ligament should reach the avascular portion of the broad ligament. The cylinder clamp which includes the uterine vessels should encircle as much parametrium as the cylinder admits. It is not necessary or even advisable to ligate the uterine vessels separately, because the transfixing needle is likely to strike a blood vessel and thus gives rise to an annoying hemorrhage.

To avoid the risk of damaging the ureter, the cylinder clamp is applied close to the uterus. This is accomplished by allowing the uterine ends of the cylinder blades to slide over the anterior and posterior surfaces of the cervix, when the clamp is closed (Fig. 5, *A* and *G*, arrows). According to Corning,[1] the distance between the ureter and the uterus in the middle of the cervix is from 8 to 25 mm. He made a series of measurements on cadavers, the ureter in the normal position. We may safely assume that during a hysterectomy, after the bladder has been separated from the cervix and the ureters pushed aside, the distance will be even greater. The cylinder of the clamp, which is 7 mm. long, is considered short enough to be safe for the ureter and long enough to secure the formation of a reliable stump. It should be noticed that it is possible to make the stump shorter than 7 mm. in spite of using the same clamp; this is accomplished by a very important maneuver, namely, the traction on the uterus upward and to the side. The upward traction makes the angle between the parametrium and the uterus more acute. Thus, the cylinder clamp which is correctly applied perpendicular to the margin of the tissue will not be parallel to the edge of the uterus (Fig. 5, *A* and *G*). As a result, the lateral end of the closure line which is the point for placing the suture will be closer to the edge of the uterus. The traction on the uterus to the side lengthens the tissue of the parametrium which will retract after the dissection. The difference in the length of the stretched and the retracted tissue is considerable and depends largely on the elasticity of the tissue. The result of this combined maneuver, namely, traction on the uterus upward and to the side, is not only that the ligature is applied closer to the uterus but also that the transverse cut (Fig. 5, *F* and *L*) and the resulting stump will be shorter than 7 mm.

Summarizing, there are three important maneuvers that must be executed in order to protect the ureter from being damaged:

1. Separation of the bladder and the ureters from the cervix by pushing the tissue downward and to the side after the peritoneal bladder reflexion has been dissected.
2. Traction on the uterus upward and to the side, and application of the cylinder clamp perpendicular to the edge of the parametrium (Fig. 5, *A* and *G*).
3. Sliding of the uterine end of the cylinder blades over the anterior and posterior surfaces of the cervix, thus placing the cylinder clamp very close to the uterus (Fig. 5, *A* and *G*, arrows).

Naturally, one must be prepared to encounter cases in which the anatomy presents marked aberrations from the norm, such as adhesions and scars resulting from previous operations or inflammatory diseases, manifestations of endometriosis, or intraligamentary tumors, to mention only a few. In cases of this kind, it is wisest to expose the ureter, as it is routinely done in performing a radical hysterectomy for carcinoma.

The cylinder clamp for the parametrium which follows the uterine vessels encircles as much tissue as desired. Here, again, the upward and sideward traction on the uterus and the matter of sliding the blades over the surface of the cervix are of the greatest importance. It depends largely on the circumstances of the case, how many ligatures are needed for hemostasis of the parametrium. After the uterine vessels have been ligated, the cardinal ligament is tied in one or two portions. It is advisable to apply a separate ligature to the uterosacral ligament.

The transverse cut is made, not only for the purpose of creating an artificial margin for better stump formation, but also to place the ligature of two consecutive stumps very close to each other (Fig. 3, *F*). The question arises, Is there any other way of achieving this result? A technique which we frequently use consists in passing first the needle through the previously tied stump close to its ligature and then encircling with the same needle the tissue, which must be ligated, or vice versa. This stump-stitch technique, as we call it, which dispenses with the transverse cut, is advantageously used in vaginal hysterectomy for the ligation of the parametrium and the adnexa, and in abdominal surgery for ligating the mesentery and the mesosalpinx. In the deeper regions of the pelvis, however, it has proved to be most inconvenient to pass the needle twice through the tissue in two different directions, as is necessary, if no free edge is available. The favorable retying maneuver (Fig. 4), which consists in using a placed ligature for retying the previous stump, is not possible in the stump-stitch technique, because there is no transverse cut, which permits carrying the new ligature around the previous stump. However, it should be stressed that the transverse cut is only performed if another ligature is to follow in the same plane. Therefore, no transverse cut is done after the last ligature of the parametrium has been placed. The transverse cut is not necessary for the following ligation of the uterosacral ligament because it is in a different plane and has its own natural edge.

The transverse cut is most efficiently performed with a small, narrow knife with a very long handle. It is best to have the cut start at the ligature (Fig. 3, *C*), with the back of the knife facing the tie, and then have the incision run to the separating cut along the closure line of the cylinder clamp. Stablike motions (Fig. 3, *C*, dotted lines) with the knife will readily separate the tissue which is being thinned out by the firm pressure of the edges of the cylinder blades. Special care must be taken not to cut the tied ligature or damage a dropped loop of bowel behind the parametrium.

The special instruments required for performing a total hysterectomy with this technique are: Three cylinder clamps,* a long fine hemostat to serve as ligature guide, and a small knife on a long handle, which is particularly useful for performing the transverse cut.

## Summary

The technical problems which arise in dissecting a narrow bridge of tissue have been pointed out. The disadvantage of crushing clamps has been shown. A common technical error which is responsible for many a hemorrhage has been revealed and described. The importance of the transverse cut and the proper location of the ligatures has been stressed, with particular reference to the problem of obtaining reliable stumps and avoiding unligated areas between the ligatures. The cylinder clamp has been presented; this new device

*Manufactured by Chas. Lentz and Sons, 33 S. 17 St., Philadelphia, Pa.

has made it possible to create a new technique for dissecting safely, a long, but narrow, bridge of tissue. The most important features of the new technique developed for the total hysterectomy are:

1. Embracing of the parametrium with the cylinder clamp, instead of crushing it.
2. Tying before cutting.
3. The transverse cut.
4. The extent of the transverse cut all the way to the ligature.
5. Placing of the ligatures extremely close to each other.
6. The use of the ligature guide.
7. Ligating of both uterine arteries before cutting one of them.
8. The retying maneuver.

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# MIDPELVIS DIAMETERS

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THE size and contour of the maternal pelvis are important factors in vaginal delivery. All standard textbooks give normal values of inlet and outlet diameters. X-ray pelvimetry has contributed much to classification of pelvic types and to establishment of normal pelvic diameters at all planes. Each method of x-ray pelvimetry includes measurement of midpelvic diameters in addition to those of the inlet and outlet. Those who have given much thought to pelvimetry have been impressed with the fact that midpelvic measurements are not only important, but that midplane contractions cloud the prognosis more than contractions at any other plane.

DeLee and Greenhill speak of the midpelvic plane as the smallest pelvic strait and frequently a site of contraction. Weinberg and Scadron state that the outlet measurements are not as important as those of the midplane because they are always greater than the midplane diameters. Mengert believes that almost without exception the midplane and the inlet tend to vary together so that a contraction at one plane tends to be associated with a contraction at the other. Mengert also believes that most outlet contractions are at the level of the midplane. Dyer in a survey of the x-ray measurements of one thousand patients says that the midplane contraction is more frequent than a contraction of either other plane. Auer and Simmons find that a floating head in a primipara is associated more often with a midplane contraction than with an inlet contraction. In the series reported by Savage midplane contraction was associated with dystocia in a high incidence.

X-ray pelvimetry is a very satisfactory and accurate way of determining the various diameters of the pelvis. Valuable as x-ray pelvimetry may be, it is available to only a few patients. The majority of general practitioners do not have x-ray facilities within easy reach, or they often have unsatisfactory interpretation of the films. Jones in a survey of obstetricians who are diplomates of the American Board found that only one-third placed real value on x-ray pelvimetry and that very few used it in more than 5 per cent of their patients. In many cases the cost of x-ray is a factor which limits the extent to which it is used. The fact remains that only a few pregnant women, coming to term, receive the benefit of x-ray pelvimetry. Pelvic adequacy of the remaining large group must be determined by manual measurements.

Manual pelvic measurements are absolutely fundamental in the teaching and the practice of obstetrics. The emphasis, in recent years, has been on x-ray pelvimetry. Methods for manual measurement of the midpelvis and standards for normal diameters have not kept pace with the advances in x-ray findings of this plane of the pelvis. Training in our medical schools should be such that the student is able to distinguish between the normal, the borderline, and the contracted pelvis in an office examination.

## Material

This discussion deals with the manual measurements of 600 consecutive private patients with special emphasis given to midpelvic size. Some time ago notations were started on four factors and diameters of the midpelvis in a quest for more definite information regarding the capacity of the pelvis. These notations were added to the routine manual pelvimetry. After 500 of the patients had been delivered it became apparent that the midpelvic diameters were closely related to the clinical course which the patient followed. It was then decided to make a survey of the series to correlate the midpelvic diameters with the final method of delivery and with the size of the infant. The patients who delivered during the time of the study of the survey were added to the series making a total of 600 cases.

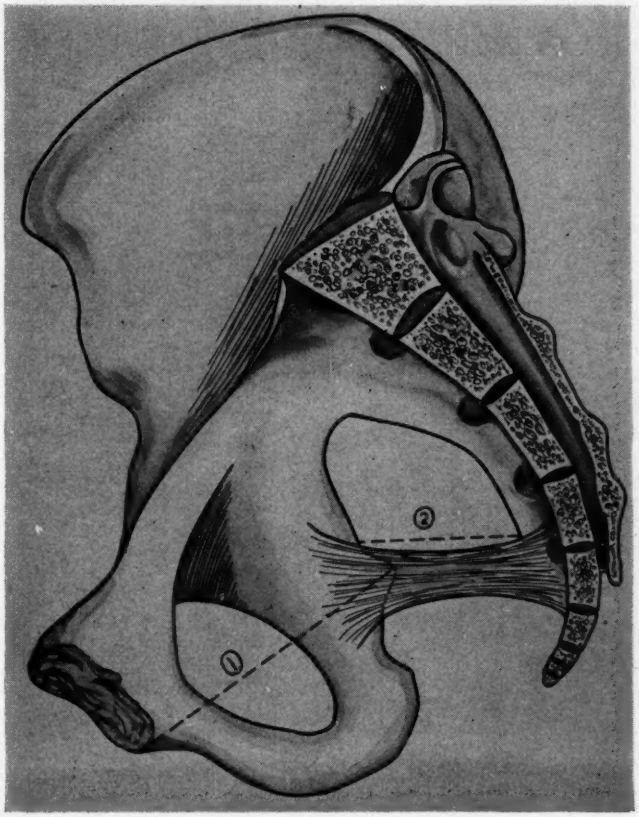


Fig. 1.—Cross section of pelvis illustrating the spinopubic diameter as line 1 and the sacrospinous diameter as line 2.

The midpelvis is measured in terms of centimeters by a method which is practical to the young physician studying obstetrics. We realize that examination of the midpelvis is not a new feature. For many years every good obstetrician has explored the midpelvis and taken abnormalities of this plane into account when evaluating the pelvis as an obstetrical risk. However, for teaching one cannot substitute a general survey of the midpelvis for direct measurements.

Manual pelvimetry should conform to several requirements: (1) It must be sufficiently simple so that measurements by different individuals are uniform. (2) It should require no elaborate equipment. (3) It should cause the

patient a minimum of discomfort. (4) It should screen out the abnormal patient whose pelvis may prove to be the cause of a cephalopelvic disproportion.

The midpelvis has four points which are easily accessible and distances between these points may be measured directly. These points are the apex of the pubic arch, the two ischial spines, and the lower end of the sacrum. The diameters to be measured are th spinopubic and the sacrospinous, illustrated in Fig. 1. In exploring the pelvis the first impression of the midpelvis is gained by the prominence of the ischial spines. The size of the spine is measured as 1+, 2+, and 3+. The largest spine is 3+ and such prominence

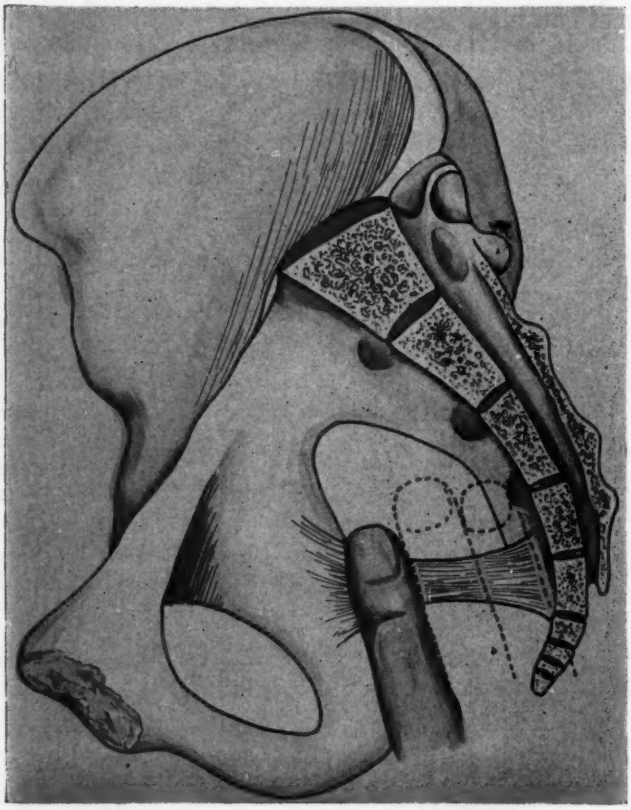

Fig. 2.—Sketch of cross section of pelvis with sacrospinous ligament being palpated in terms of fingerbreadth.

greatly reduces the transverse diameter of the midpelvis. The distance between the ischial spine and the lower end of the sacrum is synonymous with the width of the greater sciatic notch and also with the length of the sacrospinous ligament. The sacrospinous ligament or line 2 in Fig. 1 is easily palpated. A graduated sound shown in Fig. 3 may be bent at an angle 6 or 7 cm. from the tip and placed over the sacrospinous ligament for direct measurement, or fingers are placed side by side across the length of the ligament as shown in Fig. 2. The fingers are then withdrawn and the width of the fingers measured on a graduated sound. The sacrospinous diameter in this series of patients was found to vary from 4 to 6 cm. with the average diameter being 5 and 5.5 cm. A roomy sacrospinous diameter gives both depth and width to the posterior pelvis. A sacrospinous diameter of 4.5 cm. or less in-

dicates contraction of the midpelvis especially when combined with a prominent ischial spine of 3+ or 2+ size.

Anterior-posterior depth of the anterior midpelvis is obtained by measuring the distance from the apex of the pubic arch to the ischial spine or line 1 in Fig. 1. The spinopubic diameter is measured directly by the use of a graduated sound shown in Fig. 3. This diameter is found to vary from 8 to 9.5 cm. with normal range 8.5 cm. or above. A large spinopubic diameter gives valuable anterior-posterior depth to the midpelvis, but the usefulness of this space is directly proportional to the width of the pubic arch. A wide pubic arch gives full utility of this anterior sagittal triangle while an arch with an acute angle does not accommodate the head into the apex of the arch, thereby forcing the head posteriorly.

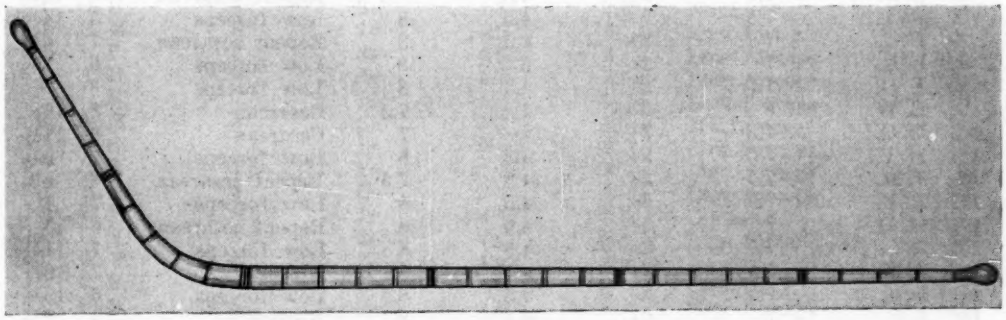

Fig. 3.—Graduated sound for direct measurement of line 1 in Fig. 1. Sound bent at other end for direct measurement of line 2 in Fig. 1.

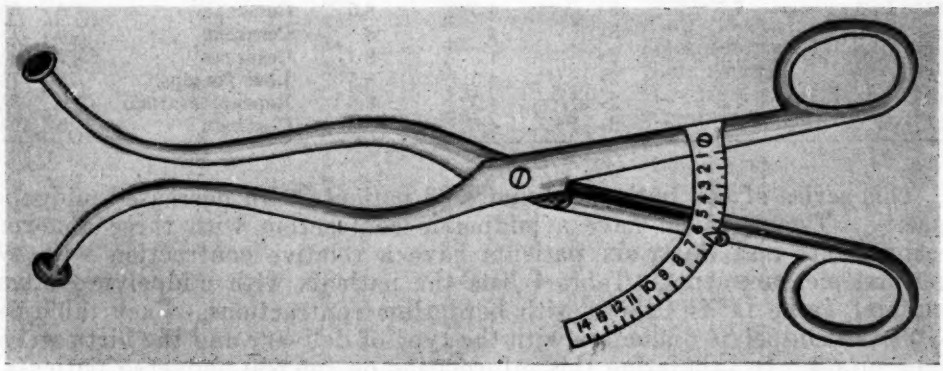

Fig. 4.—DeLee pelvimeter for direct measurement of biischial diameter.

The width of the pubic arch is a vital part of the size of the midpelvis as well as of the size of the pelvic outlet. The width of the pubic arch is measured directly by the use of the DeLee pelvimeter shown in Fig. 4. The pelvimeter is placed between the ischial tuberosities and the exact reading taken on the pelvimeter. Adding or subtracting for soft tissue only increases confusion. The biischial diameter in this series is 7 to 9.5 cm. with the average patient having a diameter of 8 to 9 cm. A diameter of 7.5 cm. or less decreases the capacity below normal.

The midpelvic measurements which indicate contraction of this plane are as follows: (1) the size of the ischial spine 2+ or larger; (2) sacrospinous diameter 4.5 cm. or less; (3) spinopubic diameter 8 cm. or less; (4) biischial diameter 7.5 cm. or less. A patient whose pelvis is characterized by three or

more abnormal measurements as given in the above group is classified as having a midpelvic contraction. A patient whose pelvic measurements contains two of the above abnormal measurements is classified as having a borderline midpelvic contraction.

TABLE I. PELVIC MEASUREMENTS, INFANT WEIGHT, AND TYPE OF DELIVERY IN 27 PATIENTS WITH THREE OUT OF FOUR MEASUREMENTS OF MIDPELVIS BELOW NORMAL

| PATIENT | BIISCHIAL (CM.) | ISCHIAL SPINE | SACRO-SPINOUS (CM.) | SPINO-PUBIC (CM.) | DELIVERY | INFANT WEIGHT (LB., OZ.) |
|---|---|---|---|---|---|---|
| 1. G. R. | 7 | 2+ | 4.5 | 8 | Normal | 5 14½ |
| 2. V. V. | 7.5 | 3+ | 4.5 | 8 | Low forceps | 8 6½ |
| 3. P. M. | 7 | 3+ | 4.5 | 8 | Low forceps | 7 6½ |
| 4. C. R. | 7.5 | 2+ | 4.5 | 7.5 | Repeat cesarean | 5 12½ |
| 5. R. A. | 7.5 | 2+ | 4.5 | 8 | Low forceps | 5 14½ |
| 6. E. C. | 7 | 2+ | 4.5 | 8 | Repeat cesarean | 7 6½ |
| 7. L. R. | 7 | 2+ | 5 | 8 | Low forceps | 6 7½ |
| 8. E. D. | 7.5 | 2+ | 4.5 | 8 | Low forceps | 8 |
| 9. E. W. | 8 | 2+ | 4 | 7.5 | Cesarean | 8 10 |
| 10. H. G. | 7.5 | 3+ | 4 | 7 | Cesarean | 6 11½ |
| 11. M. H. | 7.5 | 2+ | 4.5 | 8 | Low forceps | 7 6½ |
| 12. J. M. | 7.5 | 2+ | 4.5 | 7.5 | Repeat cesarean | 6 4¾ |
| 13. A. B. | 7.5 | 3+ | 4.5 | 8 | Low forceps | 7 7 |
| 14. M. H. | 7 | 3+ | 4.5 | 8 | Repeat cesarean | 6 15 |
| 15. E. C. | 7.5 | 2+ | 4.5 | 8 | Low forceps | 7 11½ |
| 16. J. M. | 7.5 | 2+ | 4.5 | 8 | Normal | 7 10 |
| 17. D. J. | 7.5 | 2+ | 4.5 | 8.5 | Low forceps | 6 15½ |
| 18. Z. B. | 7 | 2+ | 4.5 | 8 | Normal | 4 2½ |
| 19. J. E. | 7.5 | 3+ | 4.5 | 8.5 | Midforceps | 7 |
| 20. L. A. | 7.5 | 3+ | 4.5 | 8.5 | Low forceps | 7 14 |
| 21. V. L. | 7.5 | 2+ | 4.5 | 8.5 | Midforceps | 7 8½ |
| 22. L. A. | 7.5 | 3+ | 4.5 | 8.5 | Cesarean | 6 6½ |
| 23. G. H. | 7 | 3+ | 4 | 8 | Cesarean | 6 1¼ |
| 24. B. C. | 7.5 | 2+ | 4.5 | 8 | Cesarean | 7 9½ |
| 25. C. D. | 7.5 | 2+ | 4.5 | 8.5 | Low forceps | 6 7¾ |
| 26. A. A. | 7.5 | 2+ | 4.5 | 8.5 | Repeat cesarean | 6 3½ |
| 27. M. C. | 7 | 2+ | 4.5 | 8.5 | Cesarean | 6 10½ |

This series of 600 patients includes 63 patients with decreased midpelvic capacity. Twenty-seven have a midpelvic contraction with three abnormal measurements and thirty-six patients have a relative contraction with two abnormal measurements. Table I lists the patients with midpelvic contractions and Table II lists those with borderline contractions. Each table correlates the midpelvic diameters with the type of delivery and the birth weight of the infant. In tabulating this information on the 600 delivered patients it became evident that patients who required cesarean section for cephalopelvic disproportion had one thing in common which was that two or more of the four midpelvic measurements were abnormal. The finding of two abnormal midpelvic measurements signifies that the patient has a possible cephalopelvic disproportion if she has an infant weighing over 8 pounds. The finding of three abnormal midplane measurements signifies that the patient has a possible cephalopelvic disproportion for an infant as small as 7 pounds. No patient in this series required a cesarean section for disproportion who did not have a decreased midpelvic capacity with two or more abnormal midpelvic measurements.

Table III gives type of delivery and weight of infant in the 63 patients with decreased midpelvic size. The group of 27 midpelvic contractions was managed by doing 11 cesarean sections and 16 vaginal deliveries Seven of the patients who had vaginal deliveries were delivered of small infants weighing

less than 7 pounds. Nine patients of this group who delivered vaginally gave birth to infants weighing from 7 pounds to 8 pounds, 12 ounces, indicating that when a patient has strong contractions she will often deliver a surprisingly large infant through a small pelvis.

TABLE II. PELVIC MEASUREMENTS, INFANT WEIGHT, AND TYPE OF DELIVERY IN 36 PATIENTS WITH TWO OUT OF FOUR MEASUREMENTS OF MIDPELVIS BELOW NORMAL

| PATIENT | BIISCHIAL (CM.) | ISCHIAL SPINE | SACRO-SPINOUS (CM.) | SPINO-PUBIC (CM.) | DELIVERY | INFANT WEIGHT (LB., OZ.) |
|---|---|---|---|---|---|---|
| 1. R. S. | 8 | 2+ | 4.5 | 9 | Low forceps | 6 7½ |
| 2. J. N. | 8.5 | 2+ | 4.5 | 8.5 | Cesarean | 7 8½ |
| 3. E. H. | 8 | 3+ | 4.5 | 8.5 | Low forceps | 6 14 |
| 4. G. H. | 8 | 2+ | 4.5 | 7.5 | Normal | 4 5½ |
| 5. B. M. | 8 | 2+ | 4.5 | 8 | Low forceps | 8 6 |
| 6. L. P. | 8 | 3+ | 4.5 | 8 | Low forceps | 6 10¼ |
| 7. A. B. | 8 | 2+ | 4.5 | 8.5 | Low forceps | 7 14½ |
| 8. L. E. | 7.5 | 1+ | 4.5 | 9 | Low forceps | 7 12¾ |
| 9. A. M. | 8 | 2+ | 4.5 | 8.5 | Midforceps | 8 12½ |
| 10. A. S. | 7 | 1+ | 5 | 9 | Low forceps | 8 |
| 11. L. S. | 7.5 | 1+ | 5 | 8 | Low forceps | 6 2½ |
| 12. M. L. | 8 | 2+ | 4.5 | 8 | Low forceps | 8 4 |
| 13. E. M. | 8.5 | 1+ | 4.5 | 7.5 | Cesarean | 9 5½ |
| 14. L. N. | 8.5 | 2+ | 4.5 | 8.5 | Low forceps | 8 5 |
| 15. W. J. | 8 | 2+ | 4.5 | 8.5 | Normal | 10 |
| 16. B. B. | 8 | 2+ | 4.5 | 8 | Cesarean | 9 10 |
| 17. H. S. | 8 | 2+ | 4.5 | 8 | Low forceps | 7 6½ |
| 18. E. W. | 8 | 2+ | 4.5 | 8.5 | Low forceps | 6 8¾ |
| 19. A. D. | 7 | 2+ | 5 | 8 | Normal | 7 8 |
| 20. R. Y. | 8 | 2+ | 4.5 | 8 | Cesarean | 8 11½ |
| 21. A. S. | 8 | 2+ | 4.5 | 8 | Normal | 6 14½ |
| 22. M. G. | 7.5 | 2+ | 5 | 8.5 | Low forceps | 7 9 |
| 23. D. B. | 8 | 2+ | 4.5 | 8.5 | Low forceps | 7 14¾ |
| 24. D. F. | 7 | 2+ | 5 | 8 | Low forceps | 7 9 |
| 25. R. U. | 8 | 2+ | 4.5 | 8.5 | Low forceps | 8 6¾ |
| 26. M. H. | 7.5 | 1+ | 4.5 | 8 | Cesarean | 8 8 |
| 27. C. O. | 8 | 2+ | 4.5 | 8.5 | Normal | 7 12½ |
| 28. J. L. | 8 | 2+ | 4.5 | 8 | Low forceps | 5 4 |
| 29. A. J. | 8 | 2+ | 4.5 | 8.5 | Low forceps | 6 9 |
| 30. D. S. | 8 | 2+ | 4.5 | 8.5 | Low forceps | 6 13 |
| 31. W. D. | 8.5 | 2+ | 4.5 | 8 | Low forceps | 8 3 |
| 32. F. C. | 7.5 | 1+ | 5 | 9 | Low forceps | 6 14 |
| 33. S. S. | 8 | 3+ | 4.5 | 8 | Low forceps | 6 15½ |
| 34. D. S. | 8 | 2+ | 4.5 | 8.5 | Cesarean | 8 14½ |
| 35. E. D. | 8 | 3+ | 4 | 8.5 | Low forceps | 6 4 |
| 36. E. H. | 8.5 | 3+ | 4.5 | 8.5 | Low forceps | 6 7¾ |

TABLE III. TYPE OF DELIVERY AND INFANT WEIGHT IN 63 PATIENTS WITH DECREASED MIDPELVIC SIZE

| WEIGHT OF INFANT (POUNDS) | 27 MIDPELVIC CONTRACTIONS TYPE OF DELIVERY | | 36 BORDERLINE MIDPELVIC CONTRACTIONS TYPE OF DELIVERY | |
|---|---|---|---|---|
| | 11 CESAREAN | 16 VAGINAL | 6 CESAREAN | 30 VAGINAL |
| 7 or less | 8 | 7 | 0 | 14 |
| 7 to 8 | 2 | 8 | 1 | 8 |
| Over 8 | 1 | 1 | 5 | 8 |

The remaining six patients, delivered by cesarean section because of disproportion, came from the group of 36 patients with borderline midpelvic contractions. Five of these six patients were delivered of large infants weighing 8 pounds, 8 ounces, or larger. The sixth mother was of the type referred to

by Horner and DeLee as having the dystocia dystrophia syndrome. This patient progressed so slowly and uterine contractions were so ineffective that a cesarean section was done in the interest of the baby. The infant was delivered in good condition, weighing 7 pounds, 8½ ounces.

The seventeen patients delivered by cesarean section because of cephalopelvic disproportion may be divided into three groups. The first group includes five patients having previous cesarean section because of disproportion. The second group consists of eight primiparas each of whom had an adequate trial labor, but were not delivered vaginally because of lack of progress. The third group consists of four multiparas who were not given a trial labor because of a previous unfortunate experience of losing an infant because of cephalopelvic disproportion. Seventeen cesarean sections among six hundred patients may appear to be a high incidence but the patients of an obstetrician are not a true cross section of all pregnant patients because the obstetrician draws a larger number of abnormal cases.

The fetal loss of this series of patients is given in Table IV. Eight infants died or were stillborn, accounting for a fetal loss of 1.3 per cent. There was no infant fatality due to birth trauma. No primiparas were delivered by cesarean without a trial labor; however, each of the primiparas delivered in this manner had live healthy infants. Three infants died of erythroblastosis fetalis, one was stillborn, and two died within the first twenty-four hours of life. Two infants died of prematurity. Two infants died of congenital heart defect. One was stillborn due to intrauterine asphyxia having a true knot in the cord with the cord twice around the neck. There was no maternal mortality.

TABLE IV. FETAL LOSS

| | |
|---|---|
| Erythroblastosis | 3 |
| Prematurity | 2 |
| Congenital heart defect | 2 |
| Asphyxia | 1 |

Average and borderline manual measurements for internal pelvimetry are given below.

| | | AVERAGE | BORDERLINE |
|---|---|---|---|
| Inlet: | Diagonal conjugate | 12 to 12.5 cm. | 11 cm. |
| Midpelvis: | Sacrospinous | 5 to 5.5 cm. | 4.5 cm. |
| | Spinopubic | 8.5 to 9 cm. | 8 cm. |
| | Size of ischial spine | 1+ or flat | 2+ |
| | Pubic arch | medium or wide | narrow |
| | Biischial | 8 to 9 cm. | 7.5 cm. |

This series includes only 600 cases and is not intended to set up a standard. X-ray pelvimetry was done on some patients. The x-ray measurements and manual measurements are not taken between the same points, therefore they cannot be correlated centimeter for centimeter. However, the pelvis showing decreased size by manual measurement shows a corresponding reduction in size by x-ray measurement. All planes of the pelvis are important in considering pelvic capacity; however, the midpelvic measurements have proved of great value in screening the patients with cephalopelvic disproportion. The gynecoid and android are common pelvic types; these along with the anthropoid are congenital. In contrast, one occasionally sees the platypelloid pelvis which is an acquired characteristic. Midpelvic measurements would fail to reveal a contraction of the flat rachitic type, but with accepted pediatric care one sees fewer and fewer rachitic deformities.

This study is being continued and a further report will follow. Experience may reveal better methods of midpelvic measurement. The important fact is that careful examination and measurement of the midpelvis will add valuable information regarding the obstetrical status of the patient.

## Summary

X-ray pelvimetry has proved the value of midpelvic measurements. Many authorities are agreed that the midpelvis is the most important plane in determining pelvic adequacy. Manual midpelvic measurements have not kept abreast with x-ray advances in this field.

A series of 600 private patients with manual measurement of the midpelvis is presented. The method conforms to several fundamental prerequisites: (1) It is sufficiently simple that measurements by different individuals are uniform. (2) It requires no elaborate equipment. (3) The measurements can be taken without discomfort to the patient. (4) It screens out the patient with a possible cephalopelvic disproportion.

The midpelvic measurements taken are as follows: (1) the size of the ischial spine, (2) sacrospinous diameter, (3) spinopubic diameter, (4) width of the pubic arch.

This series reveals that about 5 per cent of the patients have a midpelvic contraction which may cause a complication if the infant's birth weight is greater than 7 pounds. An additional 5 per cent have a borderline midpelvic contraction which may not accommodate an infant larger than 8 pounds. All patients in this series having a dystocia due to cephalopelvic disproportion were among the 10 per cent who had a decreased midpelvic capacity. Many patients with a midpelvic contraction will deliver normally. Strong labor pains will overcome much dystocia due to disproportion.

The routine manual measurements with average diameters are given. An understanding of the patient's obstetrical potential is very important. Good manual measurements are a reassuring factor which add poise to the obstetrician in charge of a borderline case.

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# SURGICAL TREATMENT OF CARCINOMA OF THE CERVIX UTERI*†

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THIS paper is a report of the personal experience of the authors with the use of the radical surgical treatment for carcinoma of the cervix. Other treatments used on this service will not be discussed.

There are 50 cases in this series. They were done during the following periods:

| | | | | |
|---|---|---|---|---|
| Jan. | 1, 1944, | to Aug. | 1, 1945 | 6 cases |
| Feb. | 17, 1947, | to March | 10, 1948 | 6 cases |
| March | 10, 1948, | to June | 1, 1950 | 38 cases |

It has been felt that Meigs'[1] five reasons for doing the surgical procedure are very sound. They are:

"1. If the cervix has been removed, there is no chance for a recurrence in it.

"2. If the cervix has been removed, no cervical cancer can regrow in it as a recurrence.

"3. Certain cancers of the cervix are radiation resistant. . . .

"4. There will be less damage to the bowel if surgery is undertaken.

"5. . . . patients with lymph node metastases can be cured by surgery in some instances, and this author believes that it is not possible to cure with radiation cancer in lymph nodes deep in the pelvis."

It is felt, also, that radium before surgery would more or less "fix" the cancer cells so that spread during surgery would not occur. Interstitial application plus a cervical tandem has been the authors' choice. Seventy-five mg. were used in the cervical canal and lower fundus. Two 8 mg. needles were placed in each broad ligament, then four 6 mg. needles and four 4 mg. needles were placed in the area, and varied somewhat in pattern with the type and size of the lesion. A total of 5,000 mg. hr. was given. (The gamma roentgens at Point "A"‡ were also figured in most cases.) Surgery was done as soon as the acute vaginal reaction had subsided, which varied from 4 to 10 weeks in different individuals.

## Choice of Patients for Surgery

It has been felt that rather rigid prerequisites must be met before surgery should be done. Meigs felt that patients should be young (below 50 years),

*The opinions and/or assertions contained herein are the private ones of the writers, and are not to be construed as official or reflecting the views of the Navy Department or the Naval Service at large.

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‡Point "A" is defined as lying 2 cm. lateral to the cervical canal and 2 cm. above the mucous membrane of the lateral vaginal fornix in the axis of the uterus.

in good physical condition, thin or maybe of moderate size. He felt that obese patients should not be operated upon, but that they should be irradiated and possibly an ancillary operation, such as recommended by Taussig, carried out. He felt that not over 1 cm. of the vaginal wall should be involved. The cervix must be movable as fixation means infiltration beyond the cervix, and, although the lesion can be removed, lymphatics full of cancer cells could not be extirpated.

In the beginning of this series the authors were holding rather tenaciously to these rules. However, in the past two or three years there have been modifications. As will be seen later, the age limit has been discarded to a certain extent as long as the patient is in good physical condition. Also, obesity has been found to be less of a contraindication, and one patient operated upon some four years ago weighed 260 pounds. The operation in such a patient is technically more difficult, but not impossible. One of the prime prerequisites in this series has been good emotional stability on the part of the patient. Only one patient in this group had a vaginal extension of more than 1 cm. She had an extension into the right posterolateral wall of the vagina of 2 cm. All but 2.5 cm. of the vagina above the hymenal ring was removed, and she now has practically a dimple for a vagina but otherwise is doing nicely and there are no signs of recurrence, locally or otherwise, 34 months after operation.

Patients who have extension well out into the broad ligament (Stage III) are not, knowingly, operated upon; however, those with early extension (Stage II) are operated upon.

Stages I and II have been the cases of choice, and a few intraepithelial carcinomas, since such a high percentage of the latter showed invasion when ordinary wide hysterectomy was done. Of the cases diagnosed preoperatively as intraepithelial which have been operated upon radically, only one failed to show invasion at operation.

## Preparation of the Patient

Before any patient went to surgery, the usual meticulous study and preparation had been accomplished. The following points should be emphasized also.

1. Ureteral catheters should be inserted immediately before surgery and a bladder catheter left in place.
2. No enemas are given the 24 hours prior to surgery.
3. Anesthesia was given according to indications, but continuous spinal was the one of choice in young people with normal blood pressures, and general anesthesia was used in hypertensives and more elderly patients.

## The Operation

The patient is anesthetized and a large needle fixed securely in a good vein of the foot, and a continuous slow drip of 5 per cent glucose in distilled water is begun. Blood is used as indicated and freely to keep the patient's condition good.

The abdomen is opened by a slightly diagonal incision beginning slightly above and to the right of the umbilicus and extending to the middle of the symphysis. The round ligaments are ligated out near the internal rings and cut. The ovarian vessels are ligated bilaterally slightly above the point where the ureters pass beneath them. These are cut and the peritoneum opened from this point on the right all the way down, across the bladder reflection and up on the left side to the point where the ovarian vessels were ligated. The

bladder is then dissected off the cervix so as to leave the fascia and areolar tissue on the cervix, thus leaving the bare basket weave of vessels on the bladder. The peritoneum is then opened on the right upward along the course of the common iliac vessels to well above the aortic bifurcation. The sheath of the distal part of the aorta at a point just below the renal arteries, with its lymph nodes and channels, is circumcised and stripped downward, taking both layers of the sheath of the great vessels and all fat and areolar tissue down to the bone in the middle and from the psoas muscle laterally. Both iliac arteries and veins are cleaned to the point at which the left passes under the mesosigmoid. The presacral nodes are removed from under the mesosigmoid so as to detach it completely from the sacrum. Everything continues to be taken downward to the ureter and it is circumcised of its areolar and fat tissue and the tissue is stripped for a short distance only at that time. The ureter is left attached to the medial leaf of the peritoneum.

The external iliac vein and artery are stripped thoroughly to the femoral ring, and the fat and glands in the ring are pulled up and removed. All fat and areolar tissue are removed from the medial side of the psoas to its lower edge where the obturator nerve is found. The fat and areolar tissue about it are stripped off all the way down to the obturator foramen. During the dissection, all free tissue is carried toward the midline. The obturator foramen is then cleaned down to the bone, leaving only the obturator nerve, artery, and vein in the area. These vessels are carefully denuded of their sheaths, also. When the obturator fat has been removed, one comes up against the perivesicle fat and the dissection is continued with a clean sweep until the obliterated hypogastric artery (lateral ligament of the bladder) is reached. The dissection is then carried up the lateral ligament until it becomes the hypogastric artery; and, it is cleaned as completely as the external. The veins are likewise stripped.

As the dissection is carried down the hypogastric artery, the first noticeable branch on the medial side is found to go to the ureter. A vein is present in the area, also. These are cleaned free of areolar and fatty tissue, but preserved whenever it is possible to do so. As the dissection moves down the artery, the uterine artery is located, cut, and ligated well. There is a vesicle artery arising alongside the uterine and no efforts are made to spare it. The dissection continues down onto the bladder along the lateral side of the vagina where all tissue is removed down to the bladder pillar. Dissection is then stopped on the right side and the same procedure is carried out on the left, tunneling under the mesosigmoid to meet the previous dissection on the other side of it. When the dissection on this side is equal with that on the right, all the vessels are hanging across the pelvis like bare wires. At this point, the left ureter is cleanly stripped down to the pillar. The pillar on the left is then opened and the bare ureter dissected out, leaving all loose and fatty tissue in place. This is certainly one of the more difficult parts of the operation. The right ureter is next cleaned off and the pillar is opened and the ureter freed. If this is accomplished thoroughly, the bladder can be removed completely from the vagina as far down as necessary. The next step is to open the peritoneum transversely across the sigmoid from one longitudinal incision to the other at the level of the sacral promontory. The peritoneum across the bowel at this level is very thin and tedious to open without entering the bowel. When the peritoneum is opened thus, all loose and fatty tissue is dissected caudally to the depth of the muscular coat of the bowel. This is continued downward until the anterior leaf of the rectal sheath is found on either side. The dissection is carried out then in the prerectal space and in the pararectal space on either side. When this is carried downward sufficiently, the anterior

projections of the rectal sheath are clamped and cut as close to the bowel as is feasible. During this entire latter dissection, bleeding tends to be free and can be controlled by clamping or hot packs until ligatures are placed. The vagina is then cut across at the lowest desired site but removing at least an inch of cuff below the lowermost recognized extension of the lesion. One 4 by 4 inch piece of gauze, fluffed out, is left in the vagina from the pelvic area. This is removed at the end of 48 hours. The vagina is not suspended nor closed. All bleeding possible is controlled by ligature. Peritonization is done, and the abdomen closed with stainless steel wire through peritoneum and fascia. The skin is closed with clips.

## Postoperative Care

The aftercare is similar to that of ordinary hysterectomy cases with the following special considerations:

1. Ureteral catheters are removed in 12 to 24 hours unless a ureter obviously is injured, in which case it is removed after a minimum of 7 days. The bladder catheter is left in for 5 days.
2. Patients are allowed out of bed on the third postoperative day, unless there are complications.
3. Great care is always exercised in the insertion of the enema and rectal tubes.
4. Sulfonamides and all antibiotics are continued for five days or longer if needed.

## Lymphatic Arrangement Involved

It is equally important, if not more so, to understand the lymphatics of this area as it is to understand the anatomy. Based on the sites of extension, the nodes may be grouped into primary and secondary ones, and every effort should be made to remove these nodes as well as the intervening lymphatics. Anyone doing this type of surgery must be thoroughly familiar with these lymphatics. The distribution of these lymphatics and their nodes, both primary and secondary, may be found in any good anatomy book.

It is most important to strip every vessel down to the bare muscular wall and to remove completely all fatty and areolar tissue in the pelvis above the levator muscles, laying bare the veins and muscles of the bladder, the muscles of the rectum, the ureters, and the psoas muscles. This makes the procedure a tedious one, more liable to blood vessel hazards and more liable to urinary complications. However, it is felt by these authors that it must be done to accomplish the purpose for which the surgery is done; namely, removal of the lymphatics which may contain carcinoma cells as evidenced by this series.

## Data From Present Series of Cases

*1. Complications During Surgery.*—There were certain immediate complications which developed during surgery. Opening of the presacral venous plexus is potentially a dangerous complication, especially in the hands of the inexperienced operator, as he may continue to try ligating the veins to control the bleeding. In this series all were controlled by packing. One patient was packed with gauze and the operation stopped. The patient was returned to her room and reoperated upon four days later without further trouble with the sinus. The other immediate complications, how handled, and the results, may be noted in Table I.

*2. Complications Postoperatively.*—Urinary tract fistulas are the most dreaded of all these complications. None have been fatal but all were quite

troublesome. No attempt at surgical repair has been made under six months after they developed. There has been a total of eight such injuries, some complicated with rectal fistulas, for an uncorrected 16 per cent incidence. This is higher than the 12.3 per cent first reported by Meigs. However, five of the eight cases occurred in the hands of four neophytes in the procedure. Two patients developed fistulas on the 43rd and 49th days postoperatively, and were thought to be due to radium and/or x-ray burns. For a detailed analysis of these complications see Table I.

TABLE I. COMPLICATIONS DURING AND AFTER SURGERY

| COMPLICATION | NO. OF CASES | RESULTS |
|---|---|---|
| *During Surgery.—* | | |
| Opening of presacral venous plexus | 3 | Controlled by packing |
| Rectum opened and repaired | 1 | Good results, no fistula |
| Opening of external iliac artery | 1 | Repaired, good results |
| Opening both common iliac veins | 1 | Both ligated; moderate edema |
| Opening of one common iliac vein | 2 | Vein ligated; moderate edema |
| Injury and repair of one ureter | 1 | Good results, no fistula |
| *After Surgery.—* | | |
| Bladder paralysis 5 to 10 days | All cases | All cleared up |
| Bilateral ureterovaginal fistulas | 1 | Repaired later, good results |
| Vesicovaginal bilateral ureterovaginal, and fecal fistula | 1 | Died 92nd postoperative day |
| Ureterovaginal fistula | 3 | 2 dead kidneys, patients in good condition; 1 nephrectomy |
| Rectovesicovaginal on 49th postoperative day | 1 | Surgical repair; good results |
| Rectovaginal, ureterovaginal and fecal fistula | 1 | Nephrectomy; spontaneous closure rectovaginal and fecal fistulas |
| Ureterovaginal and rectovaginal fistulas | 1 | Dead kidney and closure of all fistulas spontaneously |
| Partial intestinal obstruction 17th postoperative day | 1 | Conservative treatment |
| Intestinal obstruction 17 months postoperatively | 1 | Surgery; only single adhesive band found |
| Abscess in pelvic "empty space" | 4 | Small and drained through vagina |
| Extraperitoneal sinus tract from pack of venus plexus | 1 | Excised |
| Deaths | 2 | 4th and 92nd postoperative days |

There were two deaths for a 4 per cent incidence. One patient died on the fourth postoperative day, rather suddenly, and at postmortem, was found to have an early partial evisceration and some bilateral pyonephrosis but it was not felt that either condition should have caused the death.

The other death was on the ninety-second postoperative day, and the postmortem examination showed rather marked bilateral pyohydronephrosis, and many adhesions from previous peritonitis when she had a fecal fistula. She had

TABLE II. COMPLICATIONS RELATIVE TO EXPERIENCE OF OPERATOR

| |
|---|
| *Four Neophyte Operators—Operated in 9 Cases—* |
| Fistulas—various combinations—5 cases for 55.5% incidence |
| Opening into presacral venous plexus—2 cases |
| Opening of external iliac artery—1 case |
| Opening of one or both common iliac veins—3 cases |
| Deaths—2 cases—all in the series |
| *Experienced Operator—Operated in 41 Cases—* |
| Fistulas—various combinations—3 cases for 7.3% incidence |
| Opened the rectum with immediate repair and good results—1 case |
| Injury to one ureter with immediate repair and good results—1 case |
| Injury to the bladder with immediate repair and good results—1 case |

had both common iliac veins ligated at the time of operation. Her course had been gradually and progressively downward after surgery.

*3. Complications Relative to Experience of the Operator.*—All these cases have been done by five operators: only the senior author had had previous experience with the procedure. As a warning and for the price of inexperience, see Table II.

These data are presented so that the operator who has not been trained for this sort of work may visualize what he faces should he boldly attempt the procedure, unless he fails to do a radical procedure. Unfortunately, for the patient and the next operator, too many people are doing very incomplete radical procedures.

## Comment

Since the majority of these patients have been operated upon only a year or two ago, it would be absurd to try to draw conclusions as to the outcome. However, certain points seem worthy of mention. All these patients are still under rigid follow-up routine and only two have developed recurrences. One developed a brain lesion 6 months after surgery and eventually came to postmortem examination. No other lesion could be found. The other had a solitary right inguinal node which was removed and nothing was found on exploring the pelvis. She has been well some nine months since the gland was removed. There are two cases of Stage III over five years, and two others three and one-half and four and one-half years, respectively, without any evidence of recurrence. During this same length of time there have been many treated with both x-ray and radium without surgery who were classed as Stage II that have had recurrence and who are now dead, while all except one classed as Stage III and so treated have died during this same period. There have been some four cases of recurrence in cases operated upon elsewhere with a less radical procedure following a full course of x-ray and radium. All four of these patients are now dead. At least the fact that these patients have shown no recurrence in the pelvis is encouraging. Donnelly and Caldwell[2] have reported no recurrences but their series is smaller and over a shorter period of time.

Undoubtedly, the lymph channels are involved whenever there are glands involved, and the fact that two with such cases are well over five years without a recurrence while two others have been well three and one-half and four and one-half years leads these writers to feel that the lymph channels can be removed, to a large extent at least, and that every effort should be made toward this aim whenever one uses radical surgery.

The incidence of fistulas as complications in this series was higher than it should be and much higher than it will be when more operators are trained. So far, these complications have not proved too difficult to handle and have been largely a nuisance though they are potentially dangerous. It is felt that, where possible, any operative repair should be delayed for a minimum of six months.

The death rate of 4 per cent in this series is not prohibitive; but here again let it be emphasized that these deaths were at the hands of inexperienced operators. Meigs has shown that the mortality can be relatively nil.

Before one feels too serene and safe from various fistulas following irradiation, one should review Everett's[3] work. In one group he reports 4 out of 13 cases treated by irradiation as having developed vesicovaginal fistulas and an associated rectovaginal fistula in two of them. This is a higher incidence of fistula than is reported here. The authors have seen some three patients recently who had been treated by irradiation who died from what was thought to be recurrences, but who, at postmortem, had only extensive irradiation damage.

The complications occurring during surgery have not proved too hazardous except in the cases where the presacral venous plexus had been opened, and in only one case was it impossible to go ahead with the surgery. Material should be available for arterial, bowel, ureter, and bladder repair. Repairs done at the time of injury have not led to complications in this series.

When the ages are reviewed, one finds a great deal of difference from the old textbook story (Table III). The youngest in this series was 21, the oldest was 58 years old.

TABLE III. MISCELLANEOUS POINTS OF INTEREST

| | NO. OF CASES |
|---|---|
| *Grade.*— | |
| I | 16 |
| II | 25 |
| III | 9 |
| *Stage.*— | |
| 0 | 1 |
| I | 25 |
| II | 15 |
| III | 9 |
| *Preoperative Irradiation.*— | |
| Radium only | 41 |
| X-ray and radium | 2 |
| None | 7 |
| *Age (years).*— | |
| Under 35 | 27, or 54% |
| 35-45 | 11, or 22% |
| Over 45 | 12, or 24% |
| *Parity.*— | |
| Para 0 | 13 |
| Para i | 13 |
| Para ii | 12 |
| Para iii | 12 |
| *Hospital Stay.*— | |
| Uncomplicated | 11.4 days, average; 8 to 17 days |
| Complicated | 33.44 days, average; 18 to 92 days |

It is rather interesting that there were essentially the same number of cases in each of the nullipara, para i, para ii, and para iii groups (Table III). This does not bear out the theory that parity increases the incidence of carcinoma of the cervix.

It has not been the policy on this service to keep the patients in bed any definite period. Some patients have asked and been allowed to get up on the first and second postoperative days. All were encouraged to get up and move about on the third postoperative day. On the third day or just as soon thereafter as tolerated they were given a regular diet. Usually the patients would take liquids the first postoperative day though parenteral fluids were given also. The second day, they were allowed a soft diet, and thereafter a regular diet was placed before them, and they were encouraged to eat as much of it as they could. This apparently prevented any lowering of the potassium level, as in all cases checked it was found to be normal. This policy paid great dividends as far as the morale and stamina of the patients were concerned. Visiting physicians remark most about the general appearance of the patients following such a procedure.

Oxycel has been discontinued on this service. There was strong evidence that it was responsible for several of the fistulas and abscesses.

It is felt that something should be said about the handling of these patients as individuals, as human beings, on this service. A policy of com-

plete frankness and honesty has been practiced, and with most gratifying results. As soon as a positive diagnosis was made, the patient and husband were interviewed by the Chief of Service at which time the patient was told exactly what she had.

The purpose of the many examinations she would undergo was thoroughly explained to her. They always asked, "What are the chances for cure?" An honest appraisal was given with the further explanation that the examinations and surgery might change our opinion, and, if so, she and her husband would be informed. The two were again interviewed about the time the patient was ready for discharge, and the pathology report was given with the latest prognosis on her case. If a fistula had developed, she was not too upset about it because such a possibility had been explained to her before surgery. There were two patients in this series who attempted suicide before knowing what was wrong because they feared that they had cancer. However, after the initial interview these patients seemed extremely calm and have been excellent patients with no mention of suicide or discouragement whatsoever. It has been felt that this policy was largely responsible for the excellent follow-up. These patients have not been checked elsewhere, solely, and the reports sent back, but rather they have reported from the East Coast, Florida, Midwest, etc., for personal examination. These patients feel that they are being treated honestly, sincerely, and as equal partners in the fight against cancer. They discuss it freely and seem no more concerned than were it a common cold.

## Summary

1. A series of fifty cases of carcinoma of the cervix treated by radical surgery is presented. Six cases were treated from January, 1944, through July, 1945; 6 cases from Feb. 17, 1947, through March 10, 1948; and 38 cases from March 10, 1948, through May 31, 1950.

2. Choice of patients is discussed.

3. Preparation of the patient is presented.

4. A detailed description of the operation is given.

5. Postoperative care is presented.

6. The importance of the lymph nodes and lymph channels involved are discussed.

7. Data from these cases, such as complications during and after surgery, complications relative to experience of the operators, grades and stages of the disease, as well as age, blood used, parity, etc., are presented.

8. The discussion presents views and conclusions drawn from the series. Also, the question whether to tell the patient or not is discussed in the afirmative.

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# THERAPEUTIC ABORTIONS WITH A FOLIC ACID ANTAGONIST, 4-AMINOPTEROYLGLUTAMIC ACID (4-AMINO P. G. A.) ADMINISTERED BY THE ORAL ROUTE

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NELSON and Evans[6] (1949) observed an impairment of reproductive functions in rats which were kept for several months, prior to their gestation period, on a folic acid deficient diet, containing succinylsulfathiazole. They also showed that the addition of a crude folic acid antagonist to the deficient diet resulted in complete resorption of the fetuses (without any deficiency period in the mothers prior to gestation). Thiersch and Philips[10] (1950), working independently from the above-named authors, induced fetal death and absorption in mice and rats that were being kept on a normal diet. This was obtained by injecting the pregnant animals with three small doses of the potent folic acid antagonist, 4-amino P. G. A., during the first week of gestation. The experiments clearly demonstrated that the mouse and the rat fetuses are very sensitive to a folic acid deficiency, which can be rapidly induced by a potent antagonist.

## Method

After the experiments with animals, it was of interest to observe the reaction of the human fetus to the folic acid antagonist. In the selection of human cases care was taken to administer the compound only to patients who had a definite indication for a therapeutic abortion such as tuberculosis, cancer, or other illness. Therapeutic abortion was recommended in all cases by a certified diplomate of the Board of Obstetrics and Gynecology and a Board member of the respective specialty. In most cases husband and wife gave written consent to the experimental procedure, and it was understood by both patient and doctor that surgical evacuation of the uterus might become necessary in case the drug should fail to induce abortion or in the presence of complications. The drug was given only to patients less than three months pregnant. The diagnosis of pregnancy was made in all cases by history, pelvic examination, and pregnancy tests in laboratory animals (Aschheim-Zondek, Friedman, or *Rana pipiens* test on urine). The hemoglobin, total blood cells, and the differential count of the patient were checked prior to, during, and following the administration of the drug. Serial pregnancy tests were carried out on the urine on the day prior to, one day after, and seven days after, the last administration of the compound to the patients,* because we realized that chorionic hormone production could long exceed fetal death. In four patients, weekly pregnancy tests followed the last dose. All patients were ambulatory and kept under supervision of the attending specialist during the period of drug administration.

*Dosage.*—Previous experience with the compound indicated that a total dose of 6 to 12 mg. given over a period of two to five days would induce a

*4-Amino P. G. A. in a concentration of 5 mg. per liter in the urine of pregnant women does not inhibit spermatogenesis in *Rana pipiens* in the presence of chorionic hormone.

slight abdominal discomfort, and a mild depression of hematopoiesis in the mother.[1, 2, 3, 12, 13] These doses, however, were expected to be fatal to the embryos.

The patients received the drug orally. An initial dose of 2 mg. was followed by three to ten subsequent doses of 1 or 2 mg. at twelve-hour intervals. In later cases, an initial dose of 3 mg. followed by two or three doses of 3 mg. at twelve-hour intervals was also found to be effective. In Cases 2, 6, and 9 a second course of 4-amino P. G. A. was administered and well tolerated. The patients were advised to omit from their diet all foods rich in folic acid. Three patients, Nos. 2, 6, and 9, were given 20 mg. of folic acid 24 and 48 hours after the last dose of the antagonist to counteract the deficiency of the maternal organism. The age of all pregnancies was estimated according to clinical history and pregnancy tests, and conception was assumed to have occurred 14 days prior to the next expected menstrual period. Most patients with a body weight over 125 pounds and/or a fetus older than 50 days received a total dose of 12 mg. of 4-amino P. G. A., because it was evident from the experiments in mice, rats, and chickens that the older embryos are more resistant to the action of the drug.

*Toxic Effects.*—Slight abdominal discomfort, loss of appetite, and, in two instances, uterine contractions were noted by the patients during the period of administration of the drug. In Cases 2, 6, and 9, who received a second course of the drug, a mild soreness of the gums and facial acne occurred following the administration of the drug, but this vanished within a few days following two daily doses of 20 mg. of Folvite. The peripheral blood showed a mild macrocytosis, a moderate fall in hemoglobin, a decreased white blood count, and an occasional nucleated red cell. One patient complained of a moderate loss of hair on combing. Ulcerative stomatitis and diarrhea, which so often complicate prolonged 4-amino P. G. A. therapy,[1, 2, 3, 13] were never noted in this short period of administration of the drug.

## Case Histories

The detailed case histories are omitted here to save space. Pertinent data are listed in Table I. More details are given here of Cases 11 and 12 as they were therapeutic failures:

CASE 11.—*Pulmonary Tuberculosis:* The patient was aged 26 years, weight 135 pounds, gravida iv, para iii. The menarche was at the twelfth year; the menstrual cycle was 25 days with flow for 5 days. The estimated age of the embryo was 40 days. Aschheim-Zondek test was positive. The hemoglobin was 11.5 Gm. per cent, hematocrit 30, red blood count 3.69 million, white blood count 7,500.

Ten mg. 4-amino P. G. A. were given orally as follows: the first dose of 2 mg. was followed by 8 doses of 1 mg. at twelve-hour intervals. Aschheim-Zondek test was positive in 24 hours, 7, 14, and 23 days after the last dose. One day after the last dose of the drug, the hemoglobin was 11.2 Gm. per cent and the white blood count 7,500. Surgical induction of abortion on the fifty-seventh day of pregnancy was followed by expulsion of the placenta and fetus on the sixty-seventh day of pregnancy.

The crown-rump measurement of the fetus was 6.3 cm.

The crown-heel measurement was 8.3 cm., corresponding to an age of 10 weeks.

The fetus was macerated, the cranium enlarged, hydrocephalic, and collapsed.

The patient left the state and no further communication was received about her for subsequent menstrual history.

CASE 12.—*Advanced Bilateral Pulmonary Tuberculosis:* The patient was aged 22 years, weight 177 pounds, gravida v, para ii. The menarche was at 14 years of age. The menstrual cycle was 30 days with moderate flow for 3 days. The estimated age of the preg-

TABLE I

| INDICATION FOR ABORTION | AGE (YEARS) | WEIGHT (POUNDS) | MENARCHE AGE | MENSTRUAL CYCLE | GRAVIDA | PARA | ESTIMATED DAYS OF PREGNANCY ON FIRST DAY OF DRUG THERAPY | TOTAL DOSE OF DRUG IN MILLIGRAMS: FIRST COURSE | TOTAL DOSE OF DRUG IN MILLIGRAMS: SECOND COURSE | DAY OF NEGATIVE RANA PIPIENS TEST AFTER DRUG THERAPY | DRUG ADMINISTRATION: HG. GM. %: BEFORE | DRUG ADMINISTRATION: HG. GM. %: AFTER | DRUG ADMINISTRATION: W.B.C.: BEFORE | DRUG ADMINISTRATION: W.B.C.: AFTER | UTERINE EVACUATION AFTER THERAPY IN DAYS | DURATION OF PREGNANCY IN UTERO (IN DAYS) | CROWN-RUMP LENGTH OF FETUS (CENTIMETERS) | STREETER AGE IN WEEKS | MALFORMATIONS |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1. Pulmonary tuberculosis | 32 | 134 | 14 | 28/4 | iii | ii | 22 | 12 | -- | 1 | 12.0 | 11.7 | 10.2 | 8.2 | Spontaneous 8 | 32 | | | |
| 2. Congenital muscular dystrophy | 30 | 120 | 13 | 28/6 | ii | i | 25<br>30 | 12 | 12 | 2 | 12.2<br>14.8 | 14.8<br>12.8 | 6.5<br>7.2 | 7.2<br>8.0 | Spontaneous 5 | 36 | | | |
| 3. Rheumatic mitral valve | 22 | 116 | 15 | 30/4 | i | 0 | 25 | 9 | -- | 1 | 12.6 | 11.5 | 11.7 | 8.5 | Spontaneous 10 | 37 | | | |
| 4. Pulmonary tuberculosis | 27 | 113 | 13 | 29/6 | ii | 1 | 25 | 9 | -- | 1 | 14.2 | 11.1 | 11.0 | 9.2 | Spontaneous 17 | 44 | | | |
| 5. Rh sensitization | 26 | 108 | 13 | 21/4 | iii | ii | 31 | 10 | -- | 1 | 14.0 | 13.8 | 8.0 | 7.9 | Spontaneous 17 | 50 | | | |
| 6. Hodgkin's disease | 33 | 134 | 12 | 28/5 | iv | ii | 33<br>62 | 8 | 11 | 1 | 14.2<br>14.0 | 14.0<br>12.8 | 11.0<br>9.0 | 9.0<br>7.5 | Spontaneous 17 | 79 | .4 | 4.0 | |
| 7. Cancer of the thyroid | 23 | 118 | 13 | 28/3 | ii | i | 35 | 8 | -- | 2 | 14.2 | 14.4 | 11.2 | 10.0 | Spontaneous 20 | 59 | .5 | 4.0 | |
| 8. Mental illness | 29 | 135 | 12 | 28/5 | v | iv | 46 | 12 | -- | 2 | 10.8 | 11.7 | 8.4 | 6.8 | Spontaneous 30 | 79 | 1.0 | 6.5 | |
| 9. Mental illness | 26 | 110 | 14 | 29/5 | ii | i | 48<br>55 | 12 | 10 | 2 | 14.4<br>14.0 | 14.0<br>11.3 | 8.5<br>6.0 | 6.0<br>3.9 | Spontaneous 11 | 69 | 4.0 | 8.0 | |
| 10. Mental illness | 36 | 131 | 14 | 28/4 | iv | iii | 49 | 10 | -- | 1 | 10.8 | 11.7 | 10.2 | 6.8 | Spontaneous 17 | 71 | 5.5 | 9.5 | X |
| 11. Pulmonary tuberculosis | 26 | 135 | 12 | 25/5 | iv | iii | 40 | 10 | -- | -- | 11.5 | 11.2 | 7.5 | 7.5 | Surgical 15 | 67 | 6.3 | 10.0 | X |
| 12. Pulmonary tuberculosis | 22 | 177 | 14 | 30/3 | v | ii | 54 | 15 | -- | 3 | 14.0 | 11.3 | 7.5 | 5.0 | Surgical 47 | 101 | 14.0 | 15.5 | X |

nancy was 54 days at date of onset of drug therapy. The total dosage of 4-amino P. G. A. was 15 mg. administered orally in 5 doses of 3 mg. at twelve-hour intervals. The Friedman test on the day prior to the first dose was positive, but there was a negative *Rana pipiens* test 24 hours, 3 and 7 days after the last dose of 4-amino P. G. A. The urine prior to drug administration showed a trace of albumin and a few erythrocytes. The patient's white blood count fell from 7,500 to 5,000 within 48 hours after the drug administration, but recovered rapidly after two days of Folvite therapy of 20 mg. per day. The patient had subsequently two further operations on the lungs which were tolerated without complications. Before the patient was sent home the gynecological examination revealed an increase in the size of the uterus corresponding to a 3½ months' pregnancy. The *Rana pipiens* test was found to be positive and it was decided to evacuate the uterus surgically.

Forty-seven days following the 4-amino P. G. A. administration and at the one hundred first day of the calculated pregnancy the cervix was dilated. The membranes perforated, and an abortion induced. A live fetus approximately 3½ months old was found in utero. The fragments of the fetus obtained by this procedure showed a cleft palate and a harelip in the intact head.

The failure of 4-amino P. G. A. to achieve fetal death in this case is unexplained; so is the negative *Rana pipiens* test on the first, third, and seventh days following the drug administration.

This case illustrates clearly the dangers and complications one can encounter when using the drug in the third month of pregnancy.

## Results

From the description of the cases it can be seen that fetal death and spontaneous abortions occurred in 10 patients. In the other two women, the drug failed to induce fetal death, and the uteri were evacuated surgically. In both instances, live fetuses with malformations were detected (Cases 11 and 12).

In the five earliest pregnancies (Cases 1, 2, 3, 4, and 5), death and abortion of the fetuses resulted within 17 days after the administration of the drug. In the other five successful cases, the pregnancy tests on the urine became negative within 48 hours after the last dose of the drug. On pelvic examination, the sizes of the uteri were found to be unaltered and at varying intervals from 5 to 30 days complete expulsion of fetus, placenta, and decidua occurred. Complications were noted in three cases. In Case 6, the *Rana pipiens* test remained persistently positive after a course of 8 mg. of 4-amino P. G. A. A second course of 11 mg. following a rest period of 29 days resulted in a negative urine test 24 hours after the last dose. When the dead fetus was expelled, it was found to be less than 0.5 cm. in length and necrotic. This showed that the first course of 4-amino P. G. A. had been fatal but that the survival of the placenta had been responsible for the hormonal output in the urine. Cases 2 and 9 were similar. An oral course of a total of 12 mg. of 4-amino P. G. A. failed to produce a negative pregnancy test and a second course of 12 and 10 mg., respectively, of the drug was administrated. The *Rana pipiens* test became negative within 48 hours after the last dose of the drug and the patients expelled their placentas, membranes, and intact fetuses 5 and 11 days after the last dose of the drug.

Case 10, surprisingly, delivered a fetus approximately 2 to 3 weeks older than anticipated, showing a large meningoencephalocele. Both findings indicate that the fetus did not die at the time of drug administration but continued to grow with a malformation.

*Failures.*—In Cases 11 and 12 the doses of 10 and 15 mg. of 4-amino P. G. A. failed to induce fetal death. Surgical evacuation of the uterus was carried out

in Case 11 because the woman wanted to leave the hospital, and also in Case 12 because of the advanced stage of pregnancy and the possibility of a malformation induced by the drug.

*Examination of Aborted Fetuses.*—Fetal elements were obtained in eight cases. The four small fetusus (Cases 2, 6, 7, and 8) could barely be recognized, appeared to be shrunken and abnormally transparent. The other larger fetuses showed pallor. Three older embryos showed malformations; a hydrocephalus in No. 11, a meningoencephalocele in No. 10, and a cleft palate with harelip in No. 12. Because of the long period of intrauterine retention of the dead embryos and the intervening postmortem changes it was difficult to determine microscopically which organs of the fetuses were most severely damaged. Liver, adrenals, and intestinal epithelium appeared to be necrotic in most cases. The uniform sparsity of the blood-forming tissues in liver, spleen, and bone marrow was striking. In the present experiments, a negative pregnancy test in the urine was accepted as presumptive evidence of fetal death, with the knowledge that a placental polyp or retention of the placenta might give rise to a positive pregnancy test in the urine. Case 12 demonstrates how one can be misled by a negative pregnancy test. In the ten cases of spontaneous expulsion of the uterine contents, the hemorrhages did not greatly exceed the usual menstrual losses. The postabortive menstrual history was without complication in all cases followed. The menstrual cycle returned to its previous rhythm and regularity within one month.

## Comment

The action of folic acid antagonists, 4-amino P. G. A. being one of the most potent, consists in the production of a folic acid deficiency. In previous experiments with these compounds it was convincingly demonstrated that the rapidly regenerating tissues of bone marrow and intestinal epithelium were the most severely affected.[8, 9, 11] From observations in mice and rats, and now in man, one has to conclude that the tissues of the embryo in the first third of intrauterine life are even more sensitive to a folic acid deficiency than the bone marrow and intestinal epithelium of the adult. It is evident that the antagonist produces in a short time an irreversible vitamin deficiency in the fetus which is incompatible with fetal life. In mice and rats the fetuses are absorbed; in the human being, however, they are expelled. The maternal organism is only slightly affected by the antagonist in the dosage used, and recovers within a few days on a normal diet. It must be stressed here that folic acid antagonists have no contraceptive action. Inhibition of ovulation in rodents required doses bringing the animals to the brink of death.[6]

The results of the observations in animals and man show indirectly the importance of folic acid for the early embryo in the species investigated.

It is quite possible that spontaneous abortion in man or animals, the occurrence of some malformations, and in some species seasonal breeding are influenced by the amount of folic acid available to the fetus.

The dosage of 4-amino P. G. A. used in the studies described varied from 6 to 24 mg. according to the age of the embryo and body weight of the mothers. Experience in chick embryos,[4] and mice and rats,[10] indicates that even smaller doses might be effective in younger embryos. It is conceivable that very small oral doses given at the time of conception, implantation, or on the first day of the first missed menstrual period, might result in rapid fetal death in the human species. In mice and rats a birth control effect was easily obtained with the drug being used in this way.[10]

Folic acid antagonists are effective when given orally and have a slightly bitter taste. They can be administered orally to patients without their knowledge, as might be necessary in mental illness.

In case the compounds are used to produce a therapeutic abortion it is advisable to give the compounds at the earliest possible stage of pregnancy and use only such amounts of the antagonist as will show a minimum effect on the mothers. It is, however, important to give sufficient amounts of the antagonist to terminate fetal life. Insufficent dosage might induce malformations and damage to fetal tissues without killing the fetus, as demonstrated in Cases 10, 11, and 12 of this series. Any method of terminating fetal life by medication to the mother differs from the finality of a surgical evacuation of the uterus by the uncertainty of the fate of the fetus until it is expelled. Our present pregnancy tests estimating chorionic or pituitary hormones give no information about fetal life and are often found to be positive long after the death of the embryo. For this reason, three patients in this series received needlessly a second course of the drug, the fetus having already died with the first course. The very absence of an accurate pregnancy test based on fetal life limits the above-described method to cases where surgical intervention can easily be applied, thereby avoiding the risk of malformation. Urine pregnancy tests carried out 48 hours and again 7 days after the last dose of the drug might show in some cases whether or not the pregnancy has terminated. The negative *Rana pipiens* test with the urine of Case 12 three and seven days following drug administration remains unexplained and was misleading. Failure of the compound to induce fetal death might occur if the drug does not reach the fetus in sufficient concentration or amounts during the period of administration. This could occur in the presence of large folic acid storage in the organism or through failure of absorption. During the time elapsed between fetal death and the spontaneous delivery of the uterine contents, the embryos underwent partial resorption and dehydration, and the internal organs became necrotic and contracted. This resulted in a fleshy condensed mass consisting of decidua, placenta, and fetus.

The failure of the drug to induce fetal death in two cases of pulmonary tuberculosis (Cases 11 and 12) was probably due to too small a dose of 4-amino P. G. A. for the advanced pregnancies of 40 and 54 days, and for the body weights of 135 and 177 pounds. In most instances one could give a second course of the compound, as was done in Cases 2, 6, and 9, provided the pregnancy had not progressed to a stage where fetal death could be achieved only at the price of severe intoxication of the mother. As stated before, attempts to induce fetal death with the drug after the third month of pregnancy are contraindicated. The occurrence of malformations in three instances (Cases 10, 11, and 12) is highly significant. Similar lesions were reported in rats by Nelson, Asling, and Evans[5] and O'Dell and Hogan[7] and in chick embryos by Karnofsky.[4] This observation suggests the necessity for completion of the abortion once the drug has been given to a patient in order to avoid the development of defective infants or monsters.

## Summary and Conclusions

1. Oral doses of 6 to 12 mg. 4-amino P. G. A. induced fetal death in the first trimester of pregnancy followed by spontaneous delivery of the products of conception in 10 out of 12 cases treated.

2. The doses lethal to the embryos had only a slight and transitory depressing effect on the hemoglobin and white blood counts of the mothers.

3. In three instances, a second course of the drug was given needlessly because of persistent positive "pregnancy tests."

4. The lesions found in the younger fetuses were depression of hematopoiesis, necrosis of the liver, adrenals, and intestinal epithelia.

5. In three older fetuses the drug failed to produce immediate death, but apparently induced malformations of the cranium. One of these fetuses died later and was delivered spontaneously. The other two were alive when surgically removed.

6. The study shows that usage of the drug to induce abortions should in the absence of reliable pregnancy tests be limited to patients in whom surgical intervention is possible to avoid malformations.

7. The action of the drug is regarded as entirely "antifolic," indicating the importance of folic acid in the early embryonic life.

8. The probable role of a folic acid deficiency in certain spontaneous abortions, in the development of malformations, and the importance of folic acid in seasonal breeding in some species is suggested by this study.

I want to express my sincere thanks to all patients and specialists who contributed to this study and to Dr. J. M. Ruegsegger of Lederle Laboratories, Pearl River, N. Y., for the general supply of Aminopterin.

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# FULL-TERM TUBAL PREGNANCY*

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A CONSIDERABLE literature has accumulated on the subject of abdominal pregnancy, and, although few obstetricians have been personally involved in any large series of cases, the treatment is well known.

There have, however, been relatively few data assembled, or cases reported, on a condition which resembles a full-term abdominal pregnancy, namely, full-term tubal pregnancy. Probably this is because, as one of the English writers stated in reporting his case, his colleagues refused to admit the possibility of a tubal pregnancy going to term.

There have been cases reported from a number of different countries. Folet of Lille in 1895 reported a case of apparent full-term pregnancy in a tube removed fifteen years after the expected date of labor. Lejars reporting before the Society of Surgery in Paris in 1904 reported a case of full-term tubal pregnancy which was confirmed microscopically. Cameron, writing in the Lancet in 1906, quoted Vilsin as saying that in 25 of 68 cases of simultaneous pregnancy in the uterus and tube the tubal fetus went to term! This was probably a verbal report as a reference could not be found. In 1910, J. Morris reported a case which grossly appeared to be tubal but in which histological examination was not done. In 1921, Gentili of the University of Sassari reported a well-documented case, with microscopic confirmation, of a full-term tubal pregnancy operated upon after ten months of gestation. Others have been reported by a number of different authors.

Not all these cases lend themselves to completely critical analysis as most of them did not have microscopic confirmation, and the patients were operated upon anywhere from two months to fifteen years after their calculated dates of confinement. It is quite possible that some of these were of the tubo-varian, interstitial, or intraligamentous type, but there are twenty-one cases in which the gross findings, at least, seemed to justify the assumption that they were actually tubal. Eight of these had the findings confirmed microscopically but in only four were live babies recovered. In all eight the mother survived and the placenta was either partially or completely removed.

This case is the fifth in which both mother and child survived and in which the diagnosis was apparently accurate both grossly and microscopically.

This patient, A. B., a 30-year-old nullipara, was first seen in the Columbia-Presbyterian Medical Center in January, 1948, with symptoms suggesting a left pyelonephritis. This was confirmed by urine cultures and during the course of her work-up she was found to have double right ureters, a trigonitis, and polyps of the bladder. Her symptoms subsided under outpatient treatment and on March 1 she was referred to the Sloane Endocrine Clinic for a complaint of sterility. She was treated in this clinic until June 25, 1949, when she was

*Presented, by invitation, at a meeting of the New York Obstetrical Society, Jan. 8, 1952.

admitted to the hospital with symptoms of a threatened abortion of about six weeks' gestation. Her chief complaint at this time was vaginal bleeding, but on one occasion she did have low backache and lower abdominal cramps. At this time the uterus was also thought to contain a small fibromyoma. All symptoms subsided in four days and the patient was discharged in good condition to the Antepartum Clinic.

Her course thereafter was uneventful except for minimal vomiting until Sept. 22, 1949, when she had a sudden attack of vomiting followed by severe lower abdominal cramps, and she was again admitted to the hospital. She had no bleeding from the vagina at this time. After admission to the hospital she also began to notice some left and right flank pain. The uterus at this time was thought to be the size of a five months' gestation and the patient had some suprapubic tenderness, dysuria, and bilateral costovertebral angle tenderness. This was more marked on the right than on the left. Overnight she developed a very marked generalized abdominal distention with rebound in the right lower quadrant and tympany throughout. Urological examination at this time was negative as were abdominal films for obstruction. She was treated with sulfadiazine only and at the end of nine days was asymptomatic and without physical signs and was discharged from the hospital.

On Nov. 2, 1949, she was again admitted to the hospital with a story of generalized abdominal soreness and tenderness, radiating into the labia, for the last six days. She then developed lumbosacral ache with frequency, burning, and urgency, and "a sticking pain in the rectum." She had had normal bowel movements and vomited only once in six days. On physical examination the abdominal mass was 4 cm. above the umbilicus, the presenting part was floating, and she had left costovertebral and left flank tenderness. Urine culture showed gram-negative bacilli and gram-positive cocci. Intermittent mild nausea and occasional vomiting occurred. She was again treated as a urological problem with sulfadiazine and at the end of two weeks was asymptomatic and returned to the clinic on Nov. 15, 1949.

She was again admitted to the hospital on Dec. 7, 1949, with a history of midlumbar back pain, vomiting, shaking chills, and fever for seven hours. The only physical findings at this time were a temperature of 101.2° F. and moderate soft distention of the upper abdomen. Urine cultures were negative and the abdominal mass at this time seemed about 6 to 7 cm. above the umbilicus, heart-shaped in outline, and the presentation a breech. The most striking physical finding continued to be the upper abdominal distention and it was felt that she had a marked gastric dilatation. Accordingly, a Miller-Abbott tube was inserted. With this and rectal treatments considerable improvement in the distention was noted. A marked anemia, hemoglobin 8.8 Gm., red blood cells 3,080,000, was present. In a few days, however, the abdomen again became distended and a Miller-Abbott tube was reinserted. X-rays of the abdomen failed to reveal any evidence of obstruction. For the second time the x-ray department noted a shadow of increased homogeneous density in the pelvic cavity, suggesting a distended urinary bladder. She was maintained on transfusions and intravenous fluids with variable effects. A barium enema and x-ray revealed nothing abnormal at this time and in January she was also thought to have a very low-grade phlebitis of the right calf, which subsided under conservative treatment. Her serum protein remained rather low and no albumin was found in the urine but suddenly, on January 16, she was found to have an elevated blood pressure and marked edema of the legs. A relatively mild toxemia of pregnancy was thought to be present and induction was advised if possible, the patient being only about three weeks from the calculated date of delivery. However, pelvic examination disclosed that the cervix did not appear ready for induction, that the baby was small, and the presentation probably transverse. An external version was easily done but the head remained high and the fetus finally settled in the oblique position. Further x-rays did not show any signs of acute intestinal obstruction. Surgical opinion at this time was that the situation was not acute from a surgical point of view and that termination of the pregnancy should be accomplished before any surgical intervention was attempted. The patient was observed for two more days without much change in her general condition. At this time it was felt advisable to terminate the pregnancy by cesarean section because of the oblique position of the fetus and her apparent unsuitability for induction. Accordingly, on Jan. 27, 1950, six days before the calculated date of confinement she was prepared for cesarean section.

The anesthesia chosen for this patient was fractional-spinal because it was believed that it would be least toxic for the baby and would give a good field for surgical exploration after the baby had been removed. Difficulty was encountered in inserting the needle and later the anesthesia was changed to cyclopropane. The abdomen was entered in the routine fashion and it became immediately apparent that the pregnancy was extrauterine rather than intrauterine. The uterus, itself, lay in the left anterior portion of the pelvis and was about the size of a three months' pregnancy. It contained a 4 to 5 cm. fibroid on the anterior surface near the left horn. The left tube appeared the seat of some chronic salpingitis, and the left ovary appeared normal. The right tube appeared normal at its origin but in about 10 cm. fanned out and apparently disappeared into a large sac which lay behind and to the right of the uterus and contained the baby. There was a wide band of omental adhesions on the superior surface of this sac but there did not appear to be any large vessels in this omentum.

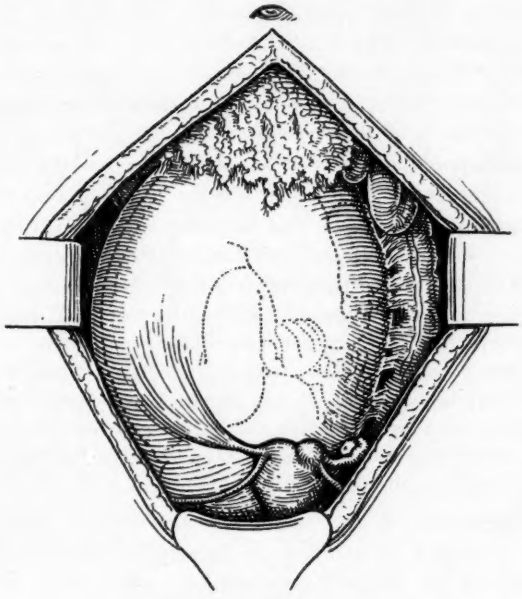

Fig. 1.—Sketch of abdominal findings.

The descending colon on the left side was adherent for almost its entire length along the left border of the sac. About 75 to 100 c.c. of extremely dark, unclotted bloody fluid were observed free in the peritoneal cavity when it was opened. A vertical incision was made in the sac, somewhat to the right of the midline, and the wall of the sac was found to be approximately the thickness of the lower uterine segment of a uterus after it has been in labor. A living male child weighing 7 pounds, 7 ounces, was extracted with ease. It seemed unusual that the wall of this sac should be so thick for an abdominal pregnancy, and in the attempt to separate the layers of the sac it became apparent that placental tissue lay within the wall of the sac. While this exploration was going on a large lobe of placenta, completely free and covered with smooth, shiny membrane, appeared from the depths of the collapsed sac and was removed manually.

The problem at this point was to determine if this was truly an abdominal pregnancy, and also what to do about the intestinal obstruction. The omentum on the superior portion of the sac was first dissected free and ligated. No placental tissue was encountered in this area. Next, the large intestine on the left side of the mass was dissected free, and again no placental tissue was encountered in this area. However, bleeding was profuse from the edges of the sac and also from the areas of dissection. At about this point the patient went into profound shock, no pulse and no blood pressure being registered by the anesthetist.

Supportive treatment in the form of transfusions under pressure was immediately begun and the patient gradually rallied. The dissection was continued around the entire circumference of the sac and at no time was there any placental tissue encountered on its external surface. On the right posterior surface of the sac the small intestine and cecum in the region of the ileocecal junction were also adherent. The dissection was continued until the sac was brought down to a neck approximately 5 cm. in diameter, apparently adherent to the right posterior portion of the uterus, and at this point it was cut across. Here definite placental tissue was found. Bleeding was profuse when this was cut across and it seemed likely that the only way of controlling this bleeding was by removal of the uterus. Accordingly, a supravaginal hysterectomy which included the adherent area of the sac on the posterior surface of the uterus was done. Multiple bleeding points in the denuded areas in the pelvis were controlled with hand and suture ligatures, and the dilated right ureter was observed in the lateral portion of the area of dissection on the right side. When all of the obvious bleeding points had been ligated, the oozing was controlled with several layers of oxidized gauze. As much peritonization as possible was done with the bladder flap, and the abdomen was closed. When the patient first went into shock she vomited fecal material and aspirated a large amount of it. It was necessary for the anesthetist to pass an endotracheal tube and suck out the bronchi.

The procedure took approximately two hours and ten minutes and she received a total of 2,000 c.c. of blood, 1,000 c.c. of saline, and 500 c.c. of 5 per cent dextrose and water. A noradrenalin infusion was begun and she was returned to the ward in fair condition. Here she was given another 1,000 c.c. of blood and the noradrenalin infusion discontinued, and her blood pressure finally stabilized at approximately 130/90. She was given large doses of Crystacillin, streptomycin, and aureomycin as well as the usual supportive treatment, and placed in an oxygen tent. Her temperature immediately postoperatively was 100.6° F. and this is the highest it went throughout her postoperative stay. Distention was controlled with rectal treatments. She was allowed out of bed on the sixth postoperative day, and was discharged in good condition with her baby on the nineteenth postoperative day. The patient was last seen May 25, 1950, four months postoperatively. She had no complaints; the pelvis was clear; and the baby was doing well.

The following is the report of microscopic findings received from Dr. Earl T. Engle:

The myometrium consisted of bundles of greatly hypertrophied smooth muscle cells. The endometrium consisted of degenerative decidua which was heavily infiltrated with lymphocytes and plasma cells. Sections through the subserous myoma showed smooth muscle and collagenous fibers in a characteristic whorled pattern. There was some hyaline degeneration.

Sections through the isthmic portion of the right tube showed the lumen to be lined by low columnar epithelium borne on low folds and rugae. The tunica propria was highly vascular and showed some decidual cells. The smooth muscle cells of this portion of the tube were greatly hypertrophied, resembling those of the corpus uteri. The blood vessels in this area were greatly enlarged. A Walthard cell rest with central cavity was also present.

Sections through more distal portions of the tube showed a normal serosa and the same hypertrophy of the smooth muscle cells of the muscular tunic. The blood vessels were greatly enlarged. The muscular media of the arteries were thickened.

Portions of the tube could be seen thinly stretched over the chorionic sac with an intact serosal surface. The smooth muscle cells, arranged in short strands, were characteristically hypertrophied. There was considerable edema in these portions of the tube, with interstitial invasion by lymphocytes and leukocytes. In one portion of this thin segment of the tube was a large blood clot. As in other portions of the tube, the blood vessels were greatly enlarged and hypertrophied.

The placenta itself presented nothing remarkable. There was a large area of infarction in one section. Fibrinoid degeneration was pronounced in all sections. The chorionic villi were characteristic of a term placenta.

The interest in this case is threefold: (1) the clinical diagnosis; (2) the pathologic diagnosis; (3) the proper treatment.

These cases are so rare that the clinician is not usually disposed to place them in the forefront of his differential diagnosis, and in this case extrauterine pregnancy was not considered. One doubt in the path of the proper diagnosis

Fig. 2.

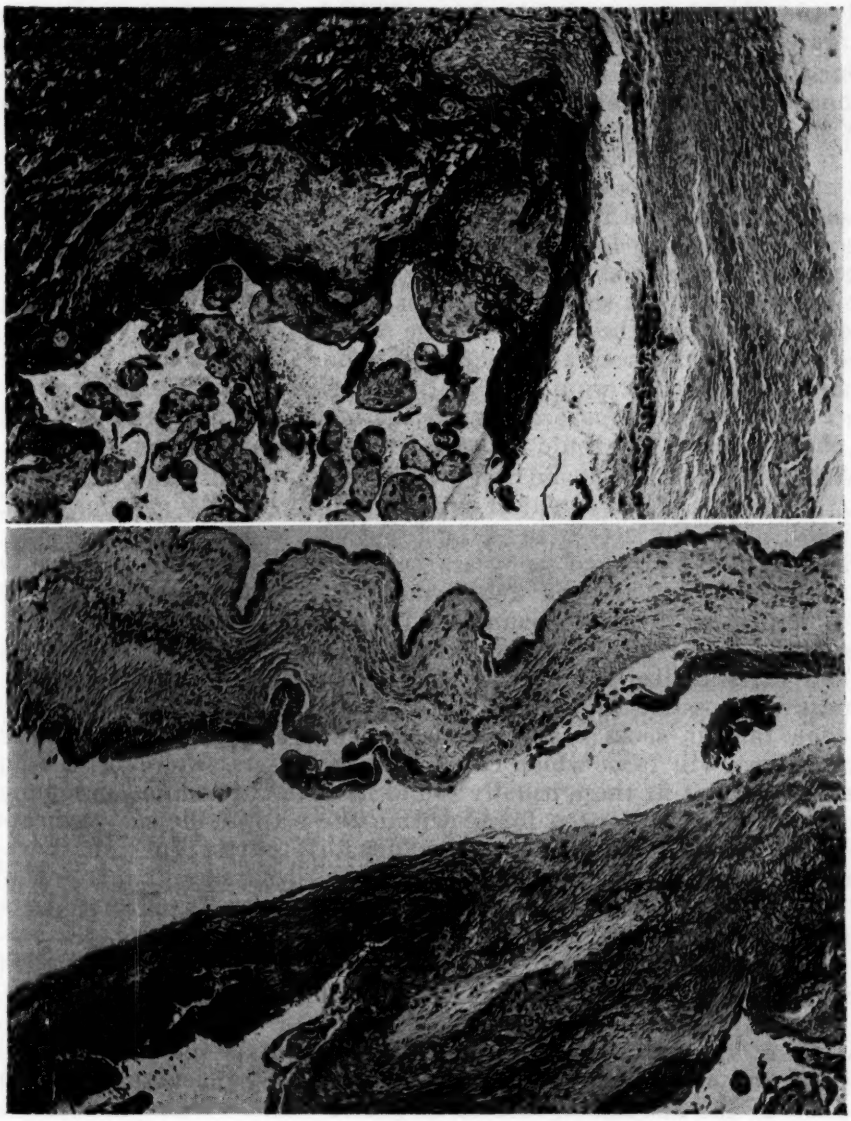

Fig. 3.

Fig. 2.—Photomicrograph showing mature placenta and tube wall.
Fig. 3.—Photomicrograph showing mature placenta and tube wall.

in this case was the presence of a congenital abnormality of the right ureter and a proved pyelonephritis before the occurrence of pregnancy. Her subsequent bizarre symptoms, falling into no systemic category and subsiding with relatively minimal treatment, all tended to obscure the diagnosis in the early

stages. The outstanding symptom of abdominal distention in the latter months should possibly have made us suspect some gestational abnormality involving the intestines, but it did not, and for this we have no excuse.

On reviewing the chart there is one clue that was missed or ignored, although its clinical evaluation would have been very difficult. This is that on four of the many x-rays taken in the evaluation of her urological and intestinal status a soft-tissue mass in the pelvis was noted and commented upon. It was usually considered a distended bladder. This should at least have been further investigated.

Once the abdomen was opened the diagnosis of extrauterine pregnancy was immediately apparent. To the operator, however, there were two confusing elements in attempting to determine *what kind* of an extrauterine pregnancy it was. In the first place, the right tube could be traced from its origin in the uterus and then seemed to fan out and amalgamate or disappear into the large sac containing the fetus. In the second place—and opening the sac could not be delayed too long for pathological rumination—the wall of the sac seemed of unexpected thickness as it was certainly 3 to 4 mm. thick and if it were a true abdominal pregnancy it should have been only the thickness of the membranes themselves. Splitting the wall of the sac soon gave the explanation, for it was at once evident that placental tissue was contained in the wall of the sac, but its external surface, which would normally have been the maternal surface of the placenta was completely covered by a smooth shiny membrane. It seemed unlikely, therefore, that this could be a real abdominal implantation of the placenta.

With this observation, and the awareness of the patient's gastrointestinal status, the problem of the extent of surgery indicated at the moment was doubly complicaed.

The operator had some ten years before assisted at an operation for abdominal pregnancy, and was aware that attempting to remove a placenta diffusely implanted in the abdominal cavity would almost certainly be attended by disastrous hemorrhage. The usual procedure followed in these cases is to pack and marsupialize the sac; or to cut the cord short, remove as much membrane as possible and close the abdomen without drainage, with the knowledge that in most cases the peritoneum will resorb the placenta or that an abscess will form which can be drained later. However, the findings in this case did not fit those usually found in a true abdominal pregnancy, for the placental tissue had been found within the wall of the sac, and, however unlikely it was for a true tubal pregnancy to progress this far, it was also questionable whether the covering membrane—whatever it was—would resorb the placenta. In addition, there was the necessity of discovering the cause of the abdominal distention.

In any event, the operator decided to attempt to remove the sac in the manner described. Although this was a bloody and hazardous procedure and would certainly have ended disastrously except for the energetic efforts of the anesthetist in the administration of supportive treatment, it was finally accomplished and at no point in the dissection was any placental tissue encountered fixed to the abdominal viscera or pelvic walls. When the sac was cut across on the posterior surface of the uterus, thin but apparently normal placental tissue was obvious. Bleeding from this cut surface made hysterectomy necessary.

In most of the cases reported the patient had progressed beyond the expected date of confinement and the fetus was dead. The placenta thereafter having undergone at least partial thrombosis and fibrosis, its removal was accompanied by less danger of hemorrhage. In abdominal pregnancies where the placenta is not removed abscess formation is well known, and in the

cases in which operation is not performed the discharge of fetal bones per rectum years later has been observed in our own hospital. Certainly, if the surgery undertaken in this case had been done in the years before blood banks the outcome for the mother would have been very dubious, and it would perhaps have been wise to have extracted only the baby.

In this case, then, the clinical diagnosis was entirely unsuspected, but on review should have been considered; the gross and microscopic findings seem to justify the rare diagnosis of full-term tubal pregnancy; and the treatment, principally the extirpation of the sac, is debatable.

I am indebted to Dr. Earl T. Engle for the microscopic examination of the specimen; to Miss Ricardo Marino for assembling the literature on this subject; to Drs. Flamingo C. Neto, Carlos Rivas, and Lysiane G. Carrette of the Department of Anesthesia and Miss Hanna Hoffman of the cytology laboratory of the Department of Obstetrics and Gynecology for their translation of the various references.

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# SAGITTAL EXPANSION IN NARROW MIDPELVES

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ACCORDING to present-day teaching, the bony pelvis is, for all practical purposes, rigid and unyielding throughout. This concept is true of all the transverse diameters, and of the sagittal diameter of the inlet, but not of the sagittal diameters of the lower pelvis. Over fifteen years ago[1] it was clearly demonstrated that marked expansion of the contracted sacropubic diameter occurs during delivery. In nineteen consecutive cases in which the sacropubic diameter was less than 9.5 cm., the enlargement amounted to 0.7 cm. to 3.0 cm., with an average of 1.8 cm. This fact is of particular significance in that it indicates that the same amount of expansion must occur in the posterior sagittal diameter of the narrow midpelvis. This is true not only because the sacropubic and posterior sagittal diameters are in close proximity and are parallel, but also because the enlargement is due to the same cause in both of these diameters, namely, the backward rotation of the sacrum.

The above observation pertaining to sagittal expansion during delivery has thus far remained unnoticed. Now that keen and widespread interest is being shown in the midpelvis, it is time to call attention once more to this important fact, and to point out its bearing on prognosis and treatment.

Before proceeding with the subject of prognosis and treatment, it should be determined to what extent sagittal expansion is necessary in transversely contracted midpelves. To accomplish this, data will first be submitted on the length of the posterior sagittal diameter in narrow midpelves. A series of deliveries will then be presented in bilaterally contracted midpelves.

## Pelvimetry

All measurements of the midpelvis were taken by means of a pelvimeter which was specifically devised for this purpose.[2, 3] The posterior end point for the posterior sagittal diameter of the midpelvis was placed at the junction of the fourth and fifth sacral segments, in accordance with the plan which was first proposed in 1938.[3] The sacropubic diameter was measured, both internally and externally, from the tip of the sacrum to the undersurface of the symphysis pubis.

## The Length of the Posterior Sagittal Diameter

It is unqualifiedly assumed that a contraction of the posterior sagittal diameter contributes to disproportion in a pelvis with a narrow bispinous diameter, and that an increase in its length compensates for such disproportion. The incidence of posterior sagittal diameters of a length which would be compensatory has, however, thus far not been determined. To obtain information on this matter a series of 124 consecutive cases with bispinous diameters of 9.5

cm. or less was accordingly reviewed. The average length of the posterior sagittal diameter in this series was found to be 5.1 cm., which is exactly 0.5 cm. less than the general average of 5.6 cm. previously reported.[3]

In 47 cases of this series in which the bispinous diameter was 9.0 cm. or less, there were only 4 cases in which the length of the posterior sagittal diameter was 6.0 cm. or over. Thus, there is only about one chance in twelve that the posterior sagittal diameter may be of sufficient length to compensate appreciably for a major contraction of the bispinous diameter. In this group of 47 cases the mean of the posterior sagittal diameter was 4.9 cm., and the variance was 0.5466 cm. The difference of 0.7 cm. between the 4.9 cm. and the general average of 5.6 cm.[3] is statistically highly significant. The correlation between the bispinous diameter and the posterior sagittal in the sample of 47 cases is 0.28. In an unrestricted sample which was previously reported[1] the incidence of bispinous diameters of 9.0 cm. or less was 5.8 per cent. On this basis the correlation between the bispinous and posterior sagittal diameters would be approximately 0.90. This high positive correlation shows that the posterior sagittal diameter would have, in most cases, a contributory rather than a compensatory effect on disproportion, which is due to transverse contraction of the midplane.

## Instrumental and Spontaneous Delivery in Bilaterally Contracted Midpelves

Data pertaining to this matter are already available in many publications.[4, 5] However, considering the importance of this subject, additional information was considered desirable. A study was accordingly made of the pathological material in a consecutive series of 908 primiparas delivered at the San Joaquin General Hospital. Among these there were 12 midforceps deliveries and 2 cesarean sections which were done for midplane contraction (Table I). Another 8 sections were done primarily for an associated contraction at the inlet.

TABLE I. MIDFORCEPS DELIVERY IN TRANSVERSELY CONTRACTED MIDPELVES WITHOUT APPARENT POSTERIOR SAGITTAL COMPENSATION (EXCEPT IN CASES 6 AND 11)

| CASE | BISPINOUS | POSTERIOR SAGITTAL | POSITION | STATION | WEIGHT OF INFANT (GRAMS) |
|---|---|---|---|---|---|
| 1 | 9.1 | 4.3 | Occipitoanterior | 4 | 3,643 |
| 2 | 9.2 | 4.6 | Occipitoposterior | 3 | 4,530 |
| 3 | 8.8 | 4.4 | Occipitoposterior | 1 | 3,409 |
| 4 | 8.5 | 4.5 | Occipitoanterior | 4 | 3,690 |
| 5 | 9.2 | 4.1 | Occipitoanterior | 3 | 3,621 |
| 6 | 8.8 | 6.8 | Occipitoposterior | 2 | 4,455 |
| 7 | 9.0 | 5.8 | Occipitoposterior | 0 | 3,977 |
| 8 | 9.0 | 4.3 | Occipitoanterior | 3 | 3,673 |
| 9 | 8.5 | 5.0 | Occipitoanterior | 3 | 3,834 |
| 10 | 8.8 | 5.0 | Occipitoposterior | 3 | 3,591 |
| 11 | 9.2 | 6.2 | Occipitoanterior | 3 | 3,636 |
| 12 | 8.8 | 4.3 | Occipitoanterior | 3 | 3,014 |
| Average | 8.9 | 4.9 | | | 3.750 |

The above series was augmented by the addition of a number of other unselected midforceps deliveries in pelves with midplane contraction. These were taken from a broken series of cases in private practice, representing a group of about 600 primiparas. In this group there were 8 midforceps deliveries (Table II) and 10 cesarean sections, but all of these sections were done primarily for inlet contraction.

In the 20 midforceps deliveries (Tables I and II) the average for the posterior sagittal diameter was 4.9 cm. This is a moderate contraction which is

the same as the general average for transversely contracted pelves, and corresponds closely to the contraction of the sacropubic diameter in the 25 midforceps deliveries which were previously reported.[1] The posterior sagittal diameter was of compensatory length in only two cases of this group. Serious difficulty resulting in a stillbirth was encountered in only one of these forceps deliveries (Case 7, Table I).

TABLE II. MIDFORCEPS DELIVERY IN TRANSVERSELY CONTRACTED MIDPELVES WITHOUT APPARENT POSTERIOR SAGITTAL COMPENSATION

| CASE | BISPINOUS | POSTERIOR SAGITTAL | WEIGHT OF INFANT (GRAMS) |
|---|---|---|---|
| 1 | 8.2 | 4.0 | 2,722 |
| 2 | 9.2 | 4.6 | 4,037 |
| 3 | 9.0 | 5.5 | |
| 4 | 8.2 | 4.9 | 4,695 |
| 5 | 9.0 | 4.7 | 3,181 |
| 6 | 9.1 | 5.2 | 4,575 |
| 7 | 8.8 | 5.5 | 3,409 |
| 8 | 9.0 | 5.2 | 3,606 |
| Average | 8.8 | 4.9 | 3,746 |

Selected cases are presented in Table III, as examples to demonstrate that uncomplicated spontaneous delivery is possible even in the presence of marked shortening of the posterior sagittal diameter (average 4.4 cm.), coupled with major transverse contraction.

TABLE III. SPONTANEOUS DELIVERY IN BILATERALLY CONTRACTED MIDPELVES

| CASE | BISPINOUS | POSTERIOR SAGITTAL | WEIGHT OF INFANT (GRAMS) |
|---|---|---|---|
| 1 | 8.5 | 3.9 | 3,666 |
| 2 | 8.8 | 4.1 | 3,379 |
| 3 | 8.8 | 4.1 | 3,241 |
| 4 | 9.0 | 3.8 | 4,198 |
| 5 | 8.5 | 4.4 | 4,037 |
| 6 | 9.2 | 4.0 | 3,409 |
| 7 | 9.2 | 3.9 | 3,181 |
| 8 | 9.0 | 4.0 | 3,041 |
| 9 | 8.2 | 5.5 | 4,067 |
| 10 | 9.2 | 4.2 | 3,726 |
| 11 | 8.2 | 5.1 | 3,576 |
| 12 | 9.0 | 5.2 | 4,665 |
| 13 | 8.8 | 4.8 | 3,211 |
| 14 | 9.0 | 4.5 | 3,211 |
| Average | 8.8 | 4.4 | 3,615 |

The deliveries listed above, taken as a whole, form a series of 34 cases. The gross disproportion in these and in similar previously reported cases,[4] would seem to be too great to be overcome by molding alone. The extent of sagittal expansion should therefore be considerable in most narrow midpelves to permit successful delivery. This inference is fully in accord with the fact, which was already stated at the beginning, namely, that there actually is marked sagittal expansion during delivery.

## A Method of Predicting the Degree of Sagittal Expansion

Considering that much may depend on expansion of the posterior sagittal diameter, it is highly desirable to have means of foretelling the degree of its

possible expansion during delivery. Fortunately, this is possible in view of the well-established fact that marked sagittal expansion of the outlet is demonstrable in the exaggerated lithotomy position at the end of pregnancy. Williams[8] found an average gain of 1.75 cm. in 106 cases, with a variation of 1.0 cm. to 2.5 cm. in 91 of these cases. Thoms[9] reported an enlargement of zero to 3.5 cm. in a series of 500 cases, with an increase of 1.0 cm. or more in 80.6 per cent of these cases.

The possible sagittal expansion of the outlet during delivery should be at least as great as that which is represented by the above data. In cases of marked disproportion the enlargement should even be greater. This may well be suspected from the observations which were made in the 19 deliveries already mentioned, in which the contracted sacropubic diameter expanded by as much as 1.8 cm., on the average. However, any amount of expansion beyond that which is revealed by the exaggerated lithotomy position must remain entirely indeterminate until additional information becomes available. Such information can be derived by comparing the extent of sagittal expansion during delivery with that which is obtained prenatally in cases of midpelvic disproportion.

The extent of sagittal expansion can be determined very simply by measuring the sacropubic diameter in the usual lithotomy position, and then again in the exaggerated lithotomy position. This can be done with an ordinary external pelvimeter according to Williams' method,[8] or with greater precision if the "Internal Outlet Pelvimeter" is used.[2] It is to be emphasized that, considering the small differences involved, experience and more than ordinary care will be required to obtain accurate and reliable measurements. The amount of sagittal expansion which is obtained in this manner, at term or during labor, is a conservative estimate of the amount of expansion which may be predicted for delivery.

## Formulary Expression of Midpelvic Contraction

Formulas have been proposed for estimating the capacity of the posterior pelvis by combining the values of the bispinous and posterior sagittal diameters. Such formulas are based on the premise that these two diameters are of identical clinical significance. This is, however, open to question. In the first place, the narrow bispinous diameter by itself strongly predisposes to the persistence of the occipitoposterior position, irrespective of the length of the posterior sagittal diameter.[6, 7] Second, the narrow bispinous diameter is responsible for diverting the passage of the largest diameter of the head behind the ischial spines, a direction which is, in itself, less favorable than the course of the normal pelvic axis, regardless of the length of the posterior sagittal diameter. Finally, the bispinous diameter is relatively constant, while the posterior sagittal is subject to considerable expansion. It seems, therefore, that more may be lost than can be gained in attempts to simplify the problem of midplane contraction by combining the bispinous and posterior sagittal diameters in one formula.

## Postural Treatment to Promote Sagittal Expansion

The exaggerated Sims position has long been recommended for outlet contraction,[8] but its value is probably due to sagittal expansion at the midplane, rather than at the outlet. The favorable effect of this position can be attributed partly to the freedom which it gives to the sacrum to rotate backward as the head advances. In the conventional dorsal position, with the sacrum impinging against the hard surface of the delivery table, there may be interference with this mechanism. A reintroduction of the now obsolete Sims position for second-stage labor may therefore be advisable for primiparas with major bilateral midpelvic contraction. A change to the dorsal position, in these cases, may well be postponed until the head is down on the perineum with the caput in sight.

## Exaggerated Axis Traction to Favor Sagittal Expansion

It has long been the practice to apply downward traction in pelves with outlet contraction,[8] but its success in the past is to be attributed to a better utilization of space in the posterior pelvis, rather than at the pelvic outlet. At present, with the shift of interest from the pelvic outlet to the midpelvis, the value of this maneuver seems to have been half-forgotten. A critical view of the problem shows, however, that if delivery is to occur through the posterior pelvis (as it must in most cases of major transverse contraction) then axis traction, or better still, *exaggerated* axis traction appears to be clearly indicated, even when the lowest part of the vertex is well below the level of the ischial spines. It seems that only by reinforced axis traction can a maximum degree of sagittal expansion be obtained, and all of the potential capacity of the posterior pelvis utilized.

Exaggerated axis traction can be obtained by a very simple maneuver: The operator applies intermittent horizontal traction with the axis traction forceps in the usual manner, while an assistant supplements this force by simultaneously exerting moderate vertical pressure on the handles of the forceps, close to the perineum. The striking effect of this maneuver in lessening resistance can be readily demonstrated by alternating exaggerated axis traction with conventional axis traction, during the same operation.

Personal experience with this method has given me uniformly gratifying results in all of the forceps deliveries listed in Tables I and II, and in a number of other midforceps deliveries with an equally restricted capacity of the posterior pelvis.

To eliminate hindrance to sagittal expansion, clearance for the sacrum can perhaps be secured by a simple device such as a thick, flat sponge-rubber pad placed under the buttocks. The use of such a device should be considered.

A disadvantage in this operation is a greater tendency to vaginal tears, and to extensions of the episiotomy. This can, however, be minimized by a deep mediolateral episiotomy extending below the level of the anus, and by the application of the downward pressure with reasonable caution, and only as long as considerable resistance is felt.

## Summary and Conclusions

The following observations are made on prognosis and treatment of labor in transversely contracted midpelves, with reference to sagittal expansion:

1. Evidence is presented which shows that sagittal expansion is a factor of sufficient importance to deserve recognition when the capacity of the posterior pelvis is estimated.

2. A method is suggested for predicting the extent of possible sagittal expansion during delivery.

3. A question is raised concerning the advisability of using formulas in which the values of the bispinous and posterior sagittal diameters are combined to represent the capacity of the posterior pelvis.

4. Emphasis is placed on the value of the exaggerated Sims position in promoting sagittal expansion.

5. Exaggerated axis traction, with clearance for the sacrum, is tentatively proposed for even low midforceps deliveries in narrow midpelves. The technique of this maneuver is outlined, and its advantages are pointed out.

I wish to express my appreciation to Raphael M. Hanson, M.A., for the statistical analysis of some of the data presented.

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# UTERINE CONTRACTIONS AT TERM AFTER ADMINISTRATION OF PROGESTERONE AND WATER-SOLUBLE EXTRACTS OF DESICCATED CORPUS LUTEUM*

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SO FAR as objective evidence goes there is no reason to believe that there is more than the one hormone, progesterone, of the corpus luteum. In clinical use, this hormone is administered most commonly in oil. In recent years, its use as a suspension of microcrystals in water, or dissolved in water by means of special saponifying substances has been attempted with a view to obtaining more rapid absorption of the hormone. Finally, a claim has been made that another water-soluble preparation made from desiccated corpus luteum tissue and not known to contain any recognized ovarian hormone is effective in reducing the amount of in vivo activity of the dog uterus.[1] The subject of the hormonal action of progesterone on the myometrium has been reviewed recently[2] and so it need not be repeated at this time.

## Method

In the present study, two aqueous preparations and one in oil were employed. A multichannel tokodynamometer was used to record extra-abdominally the activity of the uterus in the fundus and at a lower level of the uterus simultaneously. In this way, the gradient activity, the relative intensities of activity, and the frequency of contractions were recorded. The human uterus near term or in labor was used. The methods of recording are similar to those reported in previous papers.[3, 4]

As will be seen in Table I, all patients except two employed in this study, were multigravidas. Eleven women were in early or prodromal labor with the cervix in a state of little or no dilatation. Two women were in the thirty-fourth week of gestation and two were in the thirty-ninth. Membranes in all women were intact, and, in each, there was a single, normally presenting fetus. The relevant clinical and obstetrical data are given in Table I.

Three types of corpus luteum preparations were used. A conventional preparation of progesterone in oil (25 mg. per cubic centimeter, Abbott) was used in three cases. An aqueous preparation of progesterone dissolved in water (1 mg. per cubic centimeter, Squibb, lot No. BPA-82-1) with the aid of a saponifying organic substance known as Tween-80 was used in four patients. It was supplied for clinical trial only. Finally, an aqueous corpus luteum

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TABLE I

| INITIAL | AGE (YR.) | PARITY | GRAVIDITY | OBSTETRICAL STATUS | PROGRESS OF LABOR | CONTRACTIONS | | | FREQUENCY, INJECTION | CONTRACTIONS AFTER INJECTION | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | FUNDAL DOMINANCE | INTENSITY IN MM. DIVISIONS ON PAPER | AVERAGE | | FUNDAL DOMINANCE | INTENSITY IN MM. DIVISIONS ON PAPER | AVERAGE |
| G. K. | 26 | i | ii | Early labor, cervix 1 cm., full term | Delivered in 19 hours | + | 13 | 15 min. | Progesterone in oil | + | 10 | 20 min. |
| Q. H. | 26 | ii | iii | Prodromal contractions, cervix fingertip, full term | Static over 24 hours | + | 8 | 30 min. | Progesterone in oil | + | 8 | 30 min. |
| A. G. | 19 | ii | iii | Prodromal contractions at 39 weeks, cervix fingertip | Static over 24 hours | + | 13 | 25 min. | Progesterone in oil | + | 9 | 25 min. |
| J. C. | 26 | ii | iii | Early labor, cervix 3 cm. effacing | Delivered in 10 hours | + | 8 | 15 min. | Aqueous progesterone | + | 7 | 10 min. |
| D. C. | 30 | v | ix ab. iii | False labor, cervix uneffaced, full term | Static over 24 hours | + | 11 | 25 min. | Aqueous progesterone | + | 9 | 20 min. |
| R. C. | 30 | iii | v ab. i | Early labor, full term. Cervix 2 cm., effacing | Delivered in 8 hours | + | 6 | 15 min. | Aqueous progesterone | + | 6 | 15 min. |
| R. B. | 24 | iii | iv | Prodromal contractions, 34 weeks, cervix undilated | Static over 24 hours | + | 6 | 20 min. | Aqueous progesterone | + | 8 | 20 min. |
| S. C. | 20 | i | i | Early labor, cervix 2 cm., effacing | Delivered in 20 hours | + | 12 | 15 min. | Aqueous corpus luteum | + | 12 | 15 min. |
| J. P. | 29 | i | ii | Prodromal labor, cervix thick, 39 weeks | Static over 24 hours | + | 6 | 20 min. | Aqueous corpus luteum | + | 7 | 25 min. |
| Q. T. | 18 | 0 | i | Prodromal contractions, cervix thick, full term | Fine labor started in 24 hours | + | 15 | 25 min. | Aqueous corpus luteum | + | 15 | 25 min. |
| J. C. | 24 | ii | iii | Early labor, cervix 2 cm., effacing | Delivered in 13 hours | + | 13 | 10 min. | Aqueous corpus luteum | + | 12 | 10 min. |
| R. D. | 31 | v | vi | False labor, cervix uneffaced, 39 weeks | Static over 24 hours | + | 6 | 20 min. | Aqueous corpus luteum | + | 6 | 20 min. |
| D. C. | 30 | v | ix ab. iii | False labor, cervix uneffaced, full term | Static over 24 hours | + | 12 | 25 min. | Aqueous corpus luteum | + | 10 | 20 min. |
| R. C. | 30 | iii | v ab. i | Early labor, full term, cervix effacing | 14 hours to delivery | + | 8 | 15 min. | Aqueous corpus luteum | + | 10 | 12 min. |
| R. B. | 24 | iii | iv | Prodromal contractions, 34 weeks, cervix uneffaced | Static over 24 hours | + | 6 | 20 min. | Aqueous corpus luteum | + | 8 | 20 min. |

extract not known to contain progesterone was supplied by the manufacturer (Corpus Luteum Extract, Hynson, Westcott & Dunning, lot No. 7952). On the box of this preparation the following statement was made: "1 c.c. contains water-soluble extractive of 2 decigrams of fresh corpus luteum substance, which has not been heated above body temperature." The implication of this is that a labile protein complex is an active ingredient. All three preparations were administered by intramuscular injection. The dosages were: progesterone in oil, 25 mg.; progesterone in water, 2 mg.; corpus luteum extractive, 1 c.c. The quantity of progesterone administered in water is admittedly small, but larger volumes of fluid than 2 c.c. were avoided.

The effects of these substances in various phases of labor on which observations were made are as follows: fundal dominance; the frequency and rhythm of contractions; the relative intensity of contractions, particularly in the fundus; and the effect of the preparation on the course of labor. The results are summarized in Tables II and III.

TABLE II. SUMMARY OF EFFECTS

| | FREQUENCY OF CONTRACTIONS | | | RELATIVE INTENSITY OF CONTRACTIONS (FUNDUS) | | |
|---|---|---|---|---|---|---|
| | FASTER | SLOWER | UNCHANGED | INCREASED | DECREASED | UNCHANGED |
| Progesterone in oil | – | 1 | 2 | – | 2 | 1 |
| Aqueous progesterone | 2 | – | 2 | 1 | 2 | 1 |
| Aqueous corpus luteum | 2 | 1 | 5 | 3 | 2 | 3 |

TABLE III. EFFECT OF PREPARATIONS TESTED ON PATIENTS HAVING PAINFUL UTERINE CONTRACTIONS AT TERM

| | DELIVERED WITHIN 15 HOURS | DELIVERED WITHIN 15-24 HOURS | STATIC MORE THAN 24 HOURS |
|---|---|---|---|
| Progesterone in oil (25 mg.) | 0 | 1 | 1 |
| Aqueous progesterone (2 mg.) | 2 | 0 | 1 |
| Corpus luteum aqueous extract | 2 | 2 | 1 |

There was slight effect of all these preparations on the frequency of contractions and on fundal dominance. Fundal dominance existed in every case before the injection and it was unaffected afterward. The frequency of contractions was faster in two cases and it was unaffected in two women receiving progesterone in oil and one receiving the hormone in oil showed a slowing of the contraction frequency. The effects of all these substances on the organization or frequency of contractions is negligible, therefore.

The intensity of the contractions in the fundus was reduced measurably with progesterone in oil in two of three cases, and with the smaller amount of progesterone in water in two out of four cases. With the corpus luteum water-extract, there was a decrease in the intensity of contractions in two out of eight cases. In three, there was some increase in activity and three showed no change after administration of the preparation.

Ten of the fifteen patients were either in labor or were having painful but ineffective contractions at the time these observations were made. With 25 mg. of progesterone in oil, the two multigravidas in labor at the time of injection failed to deliver within fifteen hours. With 2 mg. of aqueous progesterone, two multigravidas delivered within fifteen hours and one was static for more than twenty-four hours. With the water extract of desiccated corpus luteum, two multigravidas delivered within fifteen hours, one was static for more than twenty-four hours, and two primiparous women delivered within twenty-four hours.

## Summary

The effect of progesterone in oil, aqueous progesterone, and a water-soluble extract of dried corpus luteum was examined in thirteen women at term or in labor and in two women in the thirty-fourth week of pregnancy. All patients were normal, with intact membranes and having a single conceptus. Observations were made on the relative intensity of uterine contractions, the frequency of contractions, the effect on fundal dominance, and on the course of labor.

Progesterone in oil, 25 mg. administered intramuscularly, decreased the strength of the contractions in two women and was without such effect in a third. Delivery in two multiparas in labor when receiving the hormone was delayed for 19 hours or more.

Aqueous progesterone, 2 mg., diminished the strength of contractions in two women and was without such effect in two more. Delivery in two multiparous women receiving the preparation when in labor occurred within fifteen hours, but labor was static in a third for more than twenty-four hours.

The water extractive of desiccated corpus luteum diminished activity slightly in two women but was without such an effect in six others. Two multiparous women given injections in early labor delivered within fifteen hours, two primiparous women delivered within twenty-four hours, and one multipara was static for more than twenty-four hours.

There was no effect of any of these substances on the dominance of contractility in the fundus, for it was marked at all times. The frequency of contractions was likewise unaffected.

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# VIABILITY OF HUMAN SPERMATOZOA MIXED WITH PENICILLIN G DEPOSITED IN THE FEMALE

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LONGEVITY of sperm movement is a problem which has received much discussion. In this paper I am describing a method which has produced an apparent prolongation of sperm motility.

This method involved the use of penicillin in conjunction with artificial insemination in a couple with a problem of sterility. Investigation of the wife has shown no abnormalities after the usual laboratory tests and studies for patency, ovulation, etc. Semen examinations all were normal from every aspect, as to motility, quantity, etc. However, a test done to determine how far the spermatozoa do migrate after normal intercourse showed that none had penetrated above the internal os into the uterine cavity (Weisman test[11]).

To correct this apparent abnormality and cause for the sterility, the following procedure was performed.

## Method

Artificial insemination was done and 0.5 to 1 c.c. of semen was injected into the cervix with a Cary glass cannula. The remainder of the semen specimen was deposited in the vagina. The innovation that I made was to add powdered crystalline potassium penicillin G to each specimen of semen in variable amounts from 60,000 to 100,000 units per specimen.

Rubenstein[9] was unsuccessful in preventing infection with the application of antiseptic solution to the vagina and the cervix prior to aspirating the uterine cavity. In order to avoid the possibility of injecting contaminated material from the cervix into the uterus, the following procedure was adopted:

A. Sterile powdered crystalline penicillin G was put into the bottle containing the semen specimen. The container was then shaken to produce a complete solution of the powdered penicillin in the semen.

B. All the apparatus used in these procedures was sterilized and the semen was passed by the husband into a sterile bottle.

Since the semen specimens were mixed with penicillin G, this antibiotic was depended upon to prevent infection, and so the patient was prepared before each insemination by simply washing the vagina and cervix with sterile cotton saturated with sterile physiological saline. After insemination, on withdrawing the vaginal speculum, the lower speculum blade was held at the outside of the vagina to catch the overflow of semen. This fluid was then poured into a sterile, tightly stoppered bottle, and kept at room temperature for observation of motility.

At first, the semen in the stoppered bottles was observed at frequent intervals during the day, but later it was changed to daily observations because the sperm survived so long. After insemination, with sterile glass

pipettes, the vagina and cervical canal were aspirated daily and the material examined for motile sperm. Tapering glass pipettes that entered the cervical canal for one inch were used to aspirate the cervical canal.

Six artificial inseminations were performed as described. Five studies are presented, but another one was discarded because of insufficient observations. Two of the inseminations presented did not have accompanying observations on vaginal and cervical sperm longevity. Since the patient did not conceive after these inseminations, she discontinued further studies because she was discouraged. The longevity of the sperm as detected by their motility in the vagina, high in the cervical canal, and in the stoppered bottles are shown in Fig. 1.

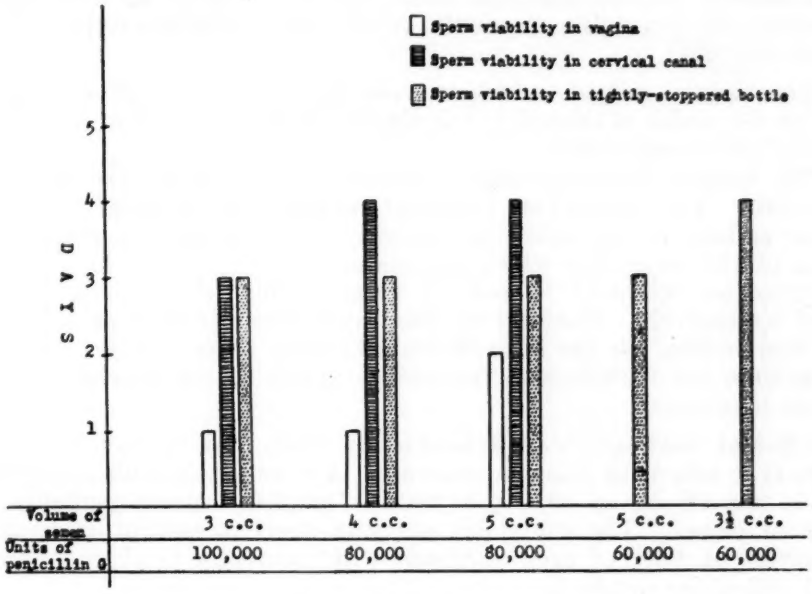


Fig. 1.

## Comment

It has been reported that seminal potency had been increased significantly in animals when penicillin was added to the semen of bulls of low fertility employed in artificial breeding.[1] In this case the penicillin was added to the semen of the husband with the hope of increasing its potency as well as avoiding the possible contamination of the endometrial cavity with the most common organisms, the pyogenic ones, on injecting the semen above the cervical mucus barrier.

Though conception did not occur in this barren couple, we cannot judge the value of penicillin with semen in barren marriage, since there were only six inseminations done and only one case was observed.

In a study by Rubenstein,[9] it was found that two out of three of his patients became infected during the five postcoital aspirations of the uterine cavities. However, in the six inseminations in which semen with penicillin G was injected into the uterus, and on the nineteen different occasions on which the cervix was aspirated one inch above the external os, *no* infection resulted. There was no febrile reaction nor inflammatory response in any of the pelvic organs following the cervical injection of sperm with penicillin G.

Cary[4] reported survival of postcoital sperm in the cervical mucus from 36 to 80 hours in four patients. The data of Huhner[7] and most recently of Cohen and Stein[5] indicate sperm survival in the cervical mucus to be generally about 48 hours.[9] The viability of sperm mixed with penicillin G was found to be 24 to 48 hours in the vagina, and as much as 96 hours high in the cervical canal on two observations. Because of the unfavorable vaginal medium, sperm, even when mixed with penicillin G, did not survive more than 48 hours.

Survival of the sperm mixed with penicillin G and kept in a tightly stoppered bottle closely approximates the survival of the spermatozoa high in the cervical canal. On two occasions, the sperm in the cervical canal outlived those out of the same original specimen kept in a tightly stoppered bottle.

The reasons for the survival of the sperm for three to four days after being mixed with crystalline penicillin G and maintained in a tightly stoppered bottle are twofold:

1. The tightly corked bottles prevent the escape of carbon dioxide and the pH of the semen is shifted to the alkaline state by a loss of base, and so a proper medium is maintained.

2. The passed semen specimen contains bacteria which are destroyed by the penicillin. The reason that bacterial growth is detrimental to sperm cells is for one or both of the following reasons: (a) The bacteria steal the sugar substrate of the semen for which the sperm vie. (b) Sperm have no protective enzyme as catalase,[6] to protect them against the hydrogen peroxide liberated by bacteria. Bacteria produce hydrogen peroxide as a by-product of their metabolism. It has been shown that three parts of hydrogen peroxide to one million are sufficient to immobilize sperm in the absence of catalase enzyme in 15 minutes.

Insufficient material was available to study the optimum amount of penicillin G to mix with a semen specimen. Yet no appreciable difference was evident in the effects of 60,000, 80,000, or 100,000 units of penicillin G per specimen of semen. The study did not lend itself to control observations of the longevity of part of each specimen with penicillin G absent, because of technical difficulties involved.

These studies on the longevity of sperm motility may have important values in the following two conditions:

1. They may give an indication for the failure of the "safe period" in the rhythm method of contraception because of the prolongation of the viability of the spermatozoa in the female genital tract due to enzymes acting similar to penicillin G.

2. The intervals between artificial insemination may be lengthened to more than one or two days because of the longer viability of the sperm.

## Summary

A method is presented which may be used to study further the viability of sperm in the female genital tract, by adding penicillin G to semen, since it appears to be free of the danger of infection to the person studied.

The longevity of spermatozoa mixed with penicillin G in the vagina and high in the cervical canal, following artificial insemination with the semen of the patient's husband, is presented. Controls for the longevity of semen mixed with penicillin G and kept in a tightly stoppered bottle are given. Comparison with studies of the longevity of sperm in cervical mucus reported in the literature show that sperm mixed with penicillin G survive longer in the cervical mucus than usually reported heretofore.

I wish to acknowledge, with appreciation, the assistance of the staff of the New York State Medical Library, Albany, N. Y., in searching the literature on this subject.

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# RENAL CONTRAINDICATIONS TO PREGNANCY

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ALTHOUGH pregnancy and labor are normal biological phenomena, they are nevertheless fraught with potential dangers and complications demanding alert and skillful medical supervision. The urinary tract plays a very important role in the female organism in its response to the varied influences of pregnancy. A history of urinary tract disease or abnormality, past or present, may greatly influence the course of pregnancy, and the physician is not infrequently called upon to determine the advisability of pregnancy, or to estimate the risk involved in such cases. It is a fortunate provision of Nature that pregnancy rarely occurs in cases in which renal deficiency has progressed to the point of nitrogen retention, but it is likely to occur in even extensive disease of one kidney.

It must be borne in mind that the kidneys have a threefold function, not only the elimination of nitrogenous waste products, but also the regulation of water balance and acid-base equilibrium, both of the latter being disturbed in pregnancy. Pregnancy is associated with a reduction of alkali reserve and acidosis may quickly supervene in severe infections of the kidneys, or other diseases which impair the total renal function.

Normal pregnancy does not impair the normal kidney function, and in general it may be stated that a degree of renal function sufficient to maintain the patient in normal health will suffice also for pregnancy and parturition. Nature has provided such a large margin of functional and anatomical renal reserve power that an individual may maintain functional equilibrium on as little as one-fourth of the total renal mass.

It is now a well-recognized fact that in every pregnancy, almost without exception, there is a condition of atony and dilatation of the upper urinary tract of varying degree in different individuals. This change is recognized as due to two factors: the pressure of the gravid uterus, the effects of which are usually more marked on the right side than on the left, and to hormonal changes causing a sponge-like softening of the tissues. Congestion and cyanosis of the tissues and general hyperemia are characteristic of the urinary organs in pregnancy. This condition continues into the puerperium for a varying period, usually with a return to normal. The atony and dilatation of the upper urinary tract result in a certain degree of urinary stasis the implications of which in pyelitis of pregnancy are self-evident. During pregnancy there is a marked increase in the frequency of bacterial invasion of the urinary tract, hence the importance of routine urine examinations at frequent intervals.

In estimating the risk of pregnancy in patients with a history of urinary tract disease or of operations on the urinary tract, the prognosis, according to Crabtree,[1] should be based on four major determinations: the nature of the previous disability, the function of the kidneys or kidney that remains, the conformation of the kidney and its drainage channels, and the presence or absence of renal disease.

In evaluating risk, a careful inquiry into the patient's history is most important. The occurrence of nephritis or acute Bright's disease in childhood, or a later period, offers a serious obstacle to pregnancy provided it has persisted into adult life. Fortunately, it often heals completely, especially in children. If at the time of pregnancy there is a normal excretion of phenolsulfonphthalein, a normal urea clearance test, a normal urine, normal dilution and concentration tests, and a normal pyelography, pregnancy is not contraindicated. The presence of albuminuria or abnormal urinary sediment usually is indicative of permanent renal damage and adds greatly to the risk of pregnancy. Pregnancy also increases the likelihood of a permanent aggravation of hypertension, if present beforehand, as well as of the nephritis itself. Rarely, albuminuria which may be termed physiological or orthostatic exists without evidence of renal damage. This is not a contraindication to pregnancy.

Various surgical diseases of the kidney including infections, stone, tuberculosis, hydronephrosis, tumor, trauma, and malformations may offer contraindications to pregnancy, but each case must be judged on its individual merits. A history of previous nephrectomy is in general no contraindication provided the remaining kidney is healthy. Nephrectomy when urgently indicated may be safely performed during pregnancy provided the opposite kidney is normal, and particularly if it has undergone compensatory hypertrophy.

Calculus disease of the kidney during pregnancy involves an increase of risk of the occurrence of pyonephrosis, so that close observation of the urine and the condition of the kidney throughout pregnancy is imperative. Intravenous urography is well tolerated during pregnancy and should be resorted to when necessary to reach a conclusion. If a calculus is diagnosed before pregnancy it should preferably be removed at that time, and if deferred the patient should be warned of its inherent danger.

Pregnancy is not contraindicated in patients who have had a kidney removed for hydronephrosis. However, the frequency with which the opposite kidney is hydronephrotic, but to a lesser degree, must be borne in mind because it can be assumed with a fair degree of certainty that the pregnancy will increase the degree of hydronephrosis already present, and that it is increasingly susceptible to infection. In a personal case in which a hydronephrotic kidney was removed, the opposite kidney was also rather markedly hydronephrotic but with adequate function. The patient went through a normal pregnancy without incident under close surveillance. During a five-year period since her pregnancy she has remained in good health and retains adequate renal function. Not in all such cases does infection occur during pregnancy but when pyelonephritis does occur the infection is usually severe and is likely to cause permanent damage.

Where one kidney has been removed for tuberculosis there is no contraindication to pregnancy provided the urinary tract is free from tuberculosis. However, if there is involvement, however slight, of the remaining kidney or even if there is any residual active infection in the bladder one should advise strongly against undertaking pregnancy. Experience proves that most of these patients eventually die of disseminated tuberculosis. The author recently performed nephrectomy for tuberculosis in the first trimester of pregnancy in a young woman with a tuberculous pyonephrosis so large that it caused a visible protrusion of her flank. However, the ureter was occluded, the voided urine was clear, and there were no active lesions in the bladder. Since this was obviously a condition of long standing, the lung fields were clear, and the patient's general health good, she was permitted to go to term.

The hypoplastic kidney as a rule offers no contraindication to pregnancy, because in general it may be considered a normal kidney of infantile proportions and has a compensatory mate. It should be differentiated from the contracted kidney of atrophic pyelonephritis.

It is a well-recognized fact that all congenital malformations and deformities of the kidneys are more likely to become pathological than the normal. The author performed nephrectomy in a woman, aged 66 years, for ectopic kidney situated deep in the pelvis behind the bladder. The kidney had been destroyed by infection and calculous disease. The patient gave a history of having gone through two normal pregnancies without complications. However, pelvic ectopic kidneys may be a cause of dystocia. Polycystic disease may not be a contraindication to pregnancy if renal function is sufficient, but in general pregnancy should be advised against because of the strong hereditary tendency exhibited by this disease.

One of the most frequent problems which demand consideration are the chronic infections of the urinary tract. Chronic pyelonephritis existing prior to pregnancy is likely to develop acute febrile phases during pregnancy. The effect of the infection in further damaging the kidneys is very great. The contraindication to pregnancy is relative rather than absolute, and demands the aid of the urologist who by careful and complete urological studies can arrive at an opinion as to whether pregnancy involves undue risk. In a personal case, the patient, 28 years of age, was recently delivered by cesarean section because of symptoms of toxemia. She had advanced chronic bilateral pyelonephritis which no amount of medication or renal lavage could eradicate prior to pregnancy. Her total renal function was greatly reduced but not to the point of nitrogen retention. The danger inherent in such a case is obvious, and an absolute contraindication to further pregnancies. It is unfortunate that this young woman's urinary tract infection could not have been apprehended in its incipiency before it had resulted in permanent damage to the kidneys. Our modern sulfonamides and antibiotics are often of no avail in advanced cases of this kind. Progressive renal damage resulted in death from uremia two years later in this case. Special attention is called to the monograph by Weiss and

Parker[2] who have emphasized the progressive nature of the destructive process in chronic pyelonephritis with an end result which cannot be clinically or pathologically differentiated from chronic Bright's disease.

Diabetes offers a relative contraindication to pregnancy. Most diabetic patients are sterile, or at least relatively infertile, so that pregnancy is of rare occurrence. The person with diabetes has not only an increased likelihood of developing pyelonephritis but also a lowered tolerance for infection. The tendency of pyelonephritis to become pyonephrosis, the frequency of occurrence of cortical sepsis and perinephritis, and the frequency of bilateral lesions of serious nature render pregnancy an extremely hazardous undertaking. The incidence of coccal infections is higher in the diabetic patient, and consequently focal suppurative nephritis involving primarily the renal cortex is more common. Since there is normally a lowering of the alkali reserve in pregnancy, the risk of uncontrollable acidosis and diabetic coma is a constant menace contraindicating pregnancy in all but the mildest forms of the disease.

## Conclusion

Where there is history of previous urinary tract disease or operation on the urinary organs the close collaboration of the obstetrician and urologist is often indicated in estimating the risk of pregnancy, and in the prevention and care of urinary tract complications which may arise during pregnancy.

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# THE USE OF DIETHYLSTILBESTROL IN THREATENED ABORTION

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THE therapy of threatened abortion has for many years consisted primarily of bed rest and sedation. With the advent of vitamins and hormone products, it was inevitable that these substances would be utilized in the problem of threatened abortion.

Progesterone in particular had good theoretical indication. Corner and Allen[1] showed it was essential for the conservation of early pregnancy, and Reynolds and Allen[2] proved its ability to inhibit uterine contractility in the rabbit. Yet, the early results with progesterone were inconclusive, possibly because the dosage used was too low from a physiologic standpoint. The possible importance of progesterone was re-emphasized when Guterman and Tulsky[3] showed that 97 per cent of the patients with low pregnandiol excretion aborted, with or without treatment. On the other hand, when pregnandiol excretion was normal, 80 per cent did not abort. Guterman concluded the dosage of 1 to 25 mg. daily at first used by him was too low, and recommended a daily intramuscular dose of 80 to 120 mg. of progesterone.

The synthetic estrogen, diethylstilbestrol, has more recently become a popular form of therapy in threatened abortion. The public has been so frequently told of the virtue of this drug through articles appearing in lay journals that it now requires a courageous physician to refuse this medication. The mass of pharmaceutical literature, extolling the wonders of this drug, has also rendered most practitioners amenable to his patient's demands. This situation, together with the understandable desire to do something positive toward rescuing a teetering pregnancy, has resulted in the widespread use of diethylstilbestrol in threatened abortion.

The two most influential papers in the medical literature giving impetus to the use of diethylstilbestrol have been written by Karnaky[4] and Smith.[5] Karnaky's original paper on this subject appeared in 1942. At that time, he stated that threatened abortion was best treated with the continuous use of diethylstilbestrol until the eighth month of pregnancy. Immediate treatment consisted of the injection of 25 mg. of diethylstilbestrol into the anterior wall of the cervix, followed by 25 mg. of the drug by mouth every fifteen minutes until all pain ceased. This was followed by 10 mg. every hour for six doses, then 5 mg. every hour for six doses, and then 10 mg. each night until the eighth month. By this technique, only 5 of 19 cases aborted. No precise definition of threatened abortion was stated and no controls were used. In a more recent paper, Karnaky[6] has increased the amount of diethylstilbestrol employed. One hundred mg. are given orally every fifteen minutes until cramps and spotting cease. Then, 25 mg. three times daily are given for a

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week, followed by a maintenance dose of 25 mg. daily until the eighth month. The histories of 21 patients are briefly reported with a fetal salvage rate of 76 per cent.

Smith's paper on this subject appeared in 1948. Her series consisted of 219 cases treated with diethylstilbestrol. Of these, 72 per cent had living children, and 78 per cent carried to the twenty-eighth week. These figures were compared favorably with Hertig's estimated spontaneous cure rate of 50 per cent. Simultaneous control studies were not carried out. All these patients exhibited vaginal bleeding beyond the date of implantation bleeding.

Other papers[7] have appeared attesting the efficiency of diethylstilbestrol in threatened abortion. However, in a well-controlled study, Crowder, Bills, and Broadbent,[8] using massive diethylstilbestrol dosage, were unable to prove the value of this drug as a panacea. With a series of 100 cases, they reported a 51 per cent salvage rate in the diethylstilbestrol-treated cases, as compared with a 57 per cent rate in controls treated by bed rest and sedation.

## Materials and Methods

Early in 1948, a carefully controlled study of threatened abortion was begun at the Sloane Hospital for Women. The criteria for a threatened abortion were established to include cases of vaginal bleeding after a missed period, with or without abdominal cramps. Cases of bleeding from the cervix itself, and cases with dilatation or effacement of the cervix were excluded after gentle and bimanual examination. The cases selected were placed alternately in either an "A" or "B" series. The "A" series was treated by diethylstilbestrol while the "B" series served as a control, without specific therapy.

All patients were hospitalized and kept on bed rest until bleeding had ceased for 24 hours. The "B" series was allowed analgesics and sedation such as phenobarbital, 30 mg. three times daily. The "A" series was given diethylstilbestrol orally as recommended by Smith[5] in a progressive dosage schedule, receiving a maximum of 125 mg. daily at the thirty-fifth week. The patients were also allowed analgesics and sedatives. Progesterone, vitamin E, and thyroid were not used as accessory medications.

A total of 112 patients was admitted for study. Fifty-seven were originally assigned to series "A," and 55 to series "B." However, it was necessary to delete 6 cases from series "A," and 13 cases from series "B." The six patients in the "A" series were excluded because 3 were not pregnant, two had no follow-up, and 1 aborted before therapy could be instituted. The 13 exclusions in series "B" were carried out because 5 cases were ectopic pregnancies, 2 had no follow-up, 2 were hydatid moles, 3 were completed abortions, and 1 was not pregnant. There remained 51 stilbestrol-treated cases ("A" series), and 42 control cases ("B" series).

Salvage studies (Table I) reveal that 11 of 51 "A" cases delivered viable infants (21 per cent), and 16 of the 42 "B" cases delivered viable infants (38 per cent).

TABLE I. COMPARISON OF FINAL RESULTS OF DIETHYLSTILBESTROL-TREATED AND CONTROL SERIES

| SERIES | NO. OF CASES | VIABLE INFANTS DELIVERED | PER CENT SALVAGED |
|---|---|---|---|
| A (Diethylstilbestrol) | 51 | 11 | 21 |
| B (Controls) | 42 | 16 | 38 |

Careful survey of the individual cases suggest that the two series were, so far as could be determined, comparable. In series "A," 3 patients aborted within 24 hours of the beginning of treatment, and, in series "B," 7 aborted

in the same period of time. In series "A," there were 4 cases of fibroids. Three of these patients aborted. In series "B," there were three cases of fibroids. Two of these patients aborted. There were three cases of placenta previa, all occurring in the "B" series. Two of these pregnancies terminated with living infants. No cases of toxemia developed in either series.

The salvage rate was higher in both series when bleeding was unaccompanied by cramps (Tables II and III), the salvage rate in series "A" rising to 36 per cent, and in series "B" to 58 per cent.

TABLE II. RESULTS IN PATIENTS HAVING BLEEDING WITHOUT CRAMPS

| SERIES | NO. OF CASES | VIABLE INFANTS DELIVERED | PER CENT SALVAGED |
|---|---|---|---|
| A (Diethylstilbestrol) | 14 | 5 | 36 |
| B (Controls) | 12 | 7 | 58 |

TABLE III. RESULTS IN PATIENTS HAVING BLEEDING WITH CRAMPS

| SERIES | NO. OF CASES | VIABLE INFANTS DELIVERED | PER CENT SALVAGED |
|---|---|---|---|
| A (Diethylstilbestrol) | 37 | 7 | 19 |
| B (Controls) | 30 | 9 | 30 |

These results give no evidence of a favorable therapeutic effect from diethylstilbestrol in threatened abortion. Total results, the salvage of 27 of 93 cases, or 29 per cent, do not compare favorably with other reported figures. Hertig and Livingstone,[9] for example, estimated that 20 per cent of all pregnancies threatened to abort with a 50 per cent spontaneous salvage. Parish[10] reported a 57 per cent salvage. Colvin and collaborators[11] reported a 70 per cent salvage rate. Rutherford,[12] however, reported only 24 of 91 threatened abortions carried to term. A possible explanation of our low figure is that all of these were clinic patients who are not likely to report bleeding and cramps as early as the patients seen in private practice.

## Comment

Various theories have been propounded as to why diethylstilbestrol should be a logical agent in the treatment of threatened abortion. The most widespread theory is that promulgated by the Smiths.[13] They believe that effective action is due to diethylstilbestrol acting like estrogenic oxidation products in causing an increased utilization of chorionic gonadotropin, which, in turn, produces an increased output of progesterone. An adequate production of progesterone is essential for the preservation of pregnancy. Heckel and Allen[14] had shown that, in the pregnant rabbit, estrogen administration had maintained progesterone secretion and delayed delivery. The Smiths demonstrated increased pregnandiol excretion following diethylstilbestrol therapy. The Smiths' contention that diethylstilbestrol caused increased progesterone formation as evidenced by increased pregnandiol excretion in the urine has been contested by Davis and Fugo.[16] Hanley[17] was also unable to show increased progesterone production with diethylstilbestrol treatment in pregnancy.

Notwithstanding the questionable modus operandi of diethylstilbestrol in threatened abortion, the high salvage rate in Smith's series (72 per cent) is an excellent attainment, and might be regarded as evidence for the use of diethylstilbestrol on purely empirical grounds. However, Colvin, Bartholomew, Grimes, and Fish[11] reported on 1,570 cases of threatened abortion

treated conservatively without hormones. Seventy per cent resulted in term babies, 2 per cent in premature deliveries, and 28 per cent aborted. These salvage figures compare favorably with those of Karnaky and Smith.

Threatened abortion is not a single disease entity. It is an expression of multiple etiological agents. It is well known that a majority of abortions are due to defective ova. Hertig and Livingstone,[9] in a study of 1,000 abortions, found 62 per cent were due to abnormal ova. Colvin and associates[11] found 86 per cent of their series aborted because of defective ova. Hertig and Rock[18] have shown that defects in the ovum are apparent even before the first missed menstrual period and thus are not amenable to therapy. The maternal factors in threatened abortion usually listed in the obstetrical textbooks include acute febrile illnesses, surgery, accompanied by sepsis and shock, x-ray therapy, trauma, anesthesia, nutritional deficiencies such as deficiencies of vitamins E, K, and C, endocrine deficiencies such as that of progesterone and thyroid, and anatomical abnormalities. The latter included submucous fibroids, endometrial polyps, previous amputation of the cervix, a septate uterus, and adherent retroversion.

Jones and Delfs[19] have shown, in studying threatened abortions, that such factors as deficient progesterone production, lowered thyroid secretion, vitamin E deficiency, uterine abnormalities, and ovular abnormalities may play a role in the abortion. It is obvious that any of these factors might play a role in an individual case of threatened abortion. To expect, on theoretical grounds, that diethylstilbestrol should remedy all these factors appears inconceivable. The present study indicates that diethylstilbestrol is, in fact, a dismal failure in the general treatment of threatened abortion.

## Conclusions

1. In a careful comparison of 51 diethylstilbestrol-treated threatened abortions with a control series of 42 untreated cases, there was no evidence that diethylstilbestrol increased the pregnancy salvage rate.

2. On account of the multiplicity of the causes leading to threatened abortion, it is hardly conceivable that one substance could serve as a panacea.

The authors desire to express their grateful appreciation of the helpful suggestions and criticisms given this project by Dr. Howard C. Taylor, Jr.

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# THE ACCURACY OF THE DIAGNOSIS OF ENDOMETRIOSIS

## A Review of 103 Cases

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THE reported incidence of endometriosis varies from a low of 1.8 per cent proved endometriosis at the Ochsner clinic (Tyrone and Weed[3]) to 28 and 30 per cent in two series of 400 private patients each as proved histologically by Meigs.[4] An intermediate incidence of 8.9 per cent was shown histologically by Kelly and Schlademan.[1] It is difficult to imagine that inherent differences in clientele could account for such great variations in the incidence of this disease. It would seem much more likely that these differences are due to errors or to difficulties in accurate diagnosis. We have found marked differences between the operative and the histological diagnosis of endometriosis in our recent cases and believe that such differences can be reduced to a minimum if better cooperation exists between the surgeon and the histopathologist.

### Material

From January, 1948, to July, 1950, there were 1,944 major operations on the Gynecologic Service at Hermann Hospital. In 103, or 5.3 per cent, of these a diagnosis of endometriosis was made. The diagnosis was based on surgical findings, histological examination, or upon both. Table I shows the number of cases diagnosed by each method. Only eight of the patients were ward or teaching cases, the remaining 95 were private patients. This is approximately the ratio between the private and teaching cases on the service.

TABLE I. BASIS OF DIAGNOSIS OF 103 CASES OF ENDOMETRIOSIS

| METHOD OF DIAGNOSIS | INCIDENCE | |
|---|---|---|
| | NO. | PER CENT |
| Surgical, only | 32 | 31.0 |
| Histological, only | 18 | 17.4 |
| Both | 53 | 51.4 |
| Total | 103 | 99.8 |

The symptoms given by the patients with histologically proved endometriosis in this series are similar in many respects to those previously reported in the literature. The average age of the patients was 35 years. The incidence of childless marriages in the group was 28 per cent. Dysmenorrhea was the most commonly encountered symptom. It was not broken down into progressive or acquired, but in 49.2 per cent of the cases there was no complaint of pain or discomfort of any type. "Flooding" or increase in the amount of the menstrual flow was a complaint in 35 per cent of the cases. In reviewing the histories it was found that 53 per cent of the patients with a histologically proved diagnosis

had previous major pelvic operative procedures. The high incidence of abdominal and pelvic surgical procedures preceding endometriosis has been reported previously. Kelly and Schlademan[1] report an incidence of 45.3 per cent and Counseller[5] reported that 43.3 per cent of his patients had had previous pelvic or abdominal surgery. Table II shows the types of previous surgery in our series.

TABLE II. TYPES AND INCIDENCE OF PREVIOUS SURGERY IN 71 CASES OF HISTOLOGICALLY PROVED ENDOMETRIOSIS

| TYPES OF SURGERY | INCIDENCE | |
|---|---|---|
| | NO. | PER CENT |
| Appendectomy, only | 14 | 20.0 |
| Adnexal surgery | 12 | 16.9 |
| Suspension | 8 | 11.2 |
| Subtotal hysterectomy | 1 | 1.4 |
| Cesarean section | 3 | 4.2 |
| No previous surgery | 33 | 46.4 |
| Total | 71 | 100.1 |

Most textbooks of gynecology give the impression that the clinical diagnosis of endometriosis is relatively simple. The symptoms and pelvic findings are described as being specific for this disease. In the review of these cases a quite different picture was found. As previously stated, 71 of the 103 cases were proved histologically. The other 32 were diagnosed grossly at the time of surgery, but not proved histologically. In this group of 71 proved cases only 33 per cent were correctly diagnosed preoperatively. Kelly and Schlademan[1] in their analysis of 179 cases report a correct diagnosis in 14.5 per cent of their cases. All these figures are based on cases with symptoms severe enough to require surgery. If all patients treated medically in the office or as outpatients could be included there is little doubt that the error in diagnosis would be even greater.

In reviewing these cases one finding seemed to stand out. This was the great difference between the number of cases diagnosed grossly at surgery and the number proved histologically. This seemed to be one error which could be easily corrected. Out of the 103 cases, 85 were diagnosed at surgery as endometriosis and of these only 53, or 62 per cent, were proved histologically. The responsibility for this difference appeared to rest equally on both the surgeon and the pathologist. The identification of endometriosis by the pathologist is often difficult, especially if the specimen has been placed in formalin or allowed to dry. The formalin discolors hemorrhagic areas of inflammatory or traumatic origin. It gives them a dark color making it difficult to distinguish them from areas of endometriosis. It also masks the distinguishing differences between inflammatory adhesions and adhesions due to endometriosis. Several other features also make identification difficult. The implants are occasionally on the serosa near its cut margin. The serosa tends to roll or wrinkle in this area thus hiding the small implants. In breaking down adhesions between areas of endometriosis and the uterine wall, the implants are frequently torn and the glands remain adherent to the uterine wall; this also makes pathological diagnosis almost impossible. It may be difficult to identify endometrial cysts histologically. This difficulty is increased if surgery is done immediately following a menstrual period. At this time the glands are very small and the cyst is markedly distended with blood. The distention causes a flattening of the epithelium and compression of the small glands. Endometrial implants may also be missed on histological section, even after gross identification by the pathologist. In a

recent case, a biopsy from an area of endometriosis on the sigmoid was sent to the pathology laboratory. The tissue was thoroughly sectioned and only two of eight sections showed glands or epithelium. This serves to illustrate how easily it can be missed if not carefully or diligently searched for.

It has been shown how easily endometriosis can be missed on histological examination, but this alone does not account for all the errors in diagnosis. The surgeon may fail to recognize it at operation, or confuse it with other pathological lesions. There were 18 cases of the 103 which were not recognized by the surgeon, but were diagnosed and proved in the pathology laboratory. The most common error in gross surgical diagnosis was an attempt to distinguish various types of hemorrhagic ovarian cysts from endometrial cysts. Curtis' textbook[2] devotes a paragraph to the difficulty in distinguishing between chocolate cysts, corpus luteum hemorrhagicum, hemorrhage into a corpus luteum cyst or into atretic follicles, and ovarian hemorrhage of other etiology. The difficulty in distinguishing these can be great, and the error tragic. Several radical procedures were done in this series, after the gross diagnosis of endometrial cysts of both ovaries. Histological diagnosis in two of these was fibrocystic ovaries with no evidence of endometriosis.

TABLE III. EXTENT OF PELVIC SURGERY PERFORMED IN CONNECTION WITH 71 CASES OF HISTOLOGICALLY PROVED ENDOMETRIOSIS

| TYPES OF SURGERY | INCIDENCE | |
|---|---|---|
| | NO. | PER CENT |
| Conservative | 17 | 24 |
| Radical | 54 | 76 |

Several members of the gynecological staff of Hermann Hospital have taken a special interest in the problem of endometriosis, and have greatly reduced this error between surgical diagnosis and histological proof. Two of these men have had 16 cases diagnosed at surgery, and 100 per cent of these were proved histologically. Although this group was small, their success is significant. These men carefully tagged areas of endometriosis seen at surgery and gave detailed descriptions to the pathology department. It is felt that by a more concentrated effort on the part of the surgeon and the pathologist a much higher percentage of cases could be proved histologically.

As a matter of secondary yet considerable importance to the patients, we show in Table III the number of conservative and radical procedures done in the series on the histologically proved cases. Cases where hysterectomy, bilateral oophorectomy, or both were done are considered radical.

Recent articles by Counseller,[5] Kelly and Schlademan,[1] Tyrone and Weed,[3] Bacon,[7] and others, have reported good results from conservative surgery in endometriosis. In our series the average age of the group undergoing conservative surgery was 29.7 years, which is much lower than the average age of the entire group. In the group who had radical surgery, nine patients were 30 years of age or younger, and ten were between 30 and 35 years of age. In this series there were thirty-two different operators so that follow-up on the cases was practically impossible.

## Summary

One hundred three cases of endometriosis which had come to surgery are reviewed. Symptomatology, incidence, and the age groups agreed rather closely with those of previously reported series. The most outstanding finding in this review was the great difference between the number of cases diagnosed at surgery

and those proved histologically. Only 62 per cent of the cases with a gross surgical diagnosis of endometriosis were proved by the pathology laboratory. It is shown that this error can be reduced by more concentrated effort.

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# USE OF ANDROGEN-ESTROGEN COMBINATION TO PREVENT PAIN AND LACTATION IN THE PUERPERIUM

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THE usefulness of either androgenic or estrogenic hormones in the suppression of lactation and relief of painful breast engorgement in the early postpartum period has frequently been reported in the literature. However, much disagreement exists as to the identity of the more effective of these hormones and as to the proper time for initiating therapy.

In the present series, study and evaluation have been made of the usefulness of an androgen-estrogen combination. This was undertaken using the rationale of the physiologic occurrence of both androgen and estrogen in normal human males and females. In the author's experience, a single injection of combined androgen-estrogen has been effective in controlling functional bleeding in 96 per cent of cases.[1] Good results have been obtained with combined hormone therapy in studies of geriatrics[2, 3] and the menopausal state.[4, 5]

Reports on the use of estrogens in suppression of lactation showed effectiveness ranging from 66 per cent[6] to 98.5 per cent.[7] Numerous side effects have been reported.[6-11] The most frequent of these is nausea and the most distressing are withdrawal bleeding and return of breast engorgement.

Testosterone has been shown to be free of such undesirable actions[12] and to have been effective in inhibiting lactation in from 60 per cent[13] to 100 per cent[14] of cases. Apparently more effective than estrogens in relief of breast engorgement, testosterone failed to accomplish this end in 6 per cent[15] to over 20 per cent[16] of cases. The exact timing of doses and the dosage are, however, matters of dispute. Arrhenomimetic effects have not been observed by investigators who employed testosterone in therapeutic dosages for the inhibition of lactation. However, the potentiality of masculinizing effects is well known and is feared by most physicians. There has been a marked hesitancy to employ testosterone in female patients, unless the condition were of such a magnitude that masculinizing effects would be unimportant in comparison.

In considering any treatment in which hormones are employed, it is simple, but not precise, to speak of "male" and "female" hormones. Both are present in individuals of either sex.[17] In addition, the gonadal hormones are not exclusively sex hormones, but exert numerous effects on extragonadal activities and psychic attitudes.

Margolese[18] observed that a specific ratio of androgen to estrogen, causing neither bleeding nor masculinization, was found to exist for each individual. Variations from this ratio were not marked, thus a specific ratio was found to be therapeutically effective for a majority of cases. The most satisfactory proportion was found to be 1 part of estradiol by weight to 20 parts of testosterone propionate. Newman[19] recently confirmed this figure. Barsantini and Masson[20] determined the relative activity of numerous steroids in lactating animals. They found estradiol to be the most active compound, followed closely

by testosterone. Since estradiol and testosterone were found to be the most biologically active steroids, and a 20:1 ratio the most physiologic proportion, we employed in our series an androgen-estrogen combination of testosterone propionate, 20 mg., plus estradiol benzoate, 1 mg. per cubic centimeter.*

Comprehensive search of the literature has failed to disclose published reports on the effect of an androgen-estrogen combination on lactation. However, studies of such combinations in menopausal therapy have brought forth several interesting facts. Glass[4] reported that the effective dosage of androgen-estrogen in combination was markedly less than that of either hormone given separately. In his series, withdrawal bleeding or andromimetic effects were rarely seen and then only after prolonged maintenance therapy. He remarked that the anabolic synergism of the androgen-estrogen combination provided an optimum sense of well-being.

With such obvious advantages in mind, we employed an androgen-estrogen combination in one series to relieve painful lactation; and, in a second series, to suppress lactation.

## Method

A parenteral preparation of androgen-estrogen (testosterone propionate, 20 mg., plus estradiol benzoate, 1 mg. per cubic centimeter) was administered to an unselected group of 50 patients. All patients received a single intramuscular injection during the first 24 hours post partum.

To establish painless lactation without suppression of the flow of milk, a single injection of 1 c.c. was administered during the first 24 hours post partum.

To inhibit lactation an injection of 2 c.c. was administered during the first 24 hours.

Two patients received an additional dose of 1 c.c.

No other treatment of any type was employed.

## Results

Of 17 patients treated to ensure painless lactation, results were good in 15 patients (88 per cent). One patient experienced minimal discomfort. In

TABLE I. RELIEF OF PAINFUL LACTATION WITH COMBINED ANDROGEN-ESTROGEN THERAPY

| PATIENT | GRAVIDA | AGE (YEARS) | DOSAGE | LACTATION | RESULTS |
|---|---|---|---|---|---|
| C. S. | i | 26 | 1 c.c. | Painless lactation | |
| F. Z. | ii | 24 | 1 c.c. | Slight pain | |
| E. M. | i | 17 | 1 c.c. | Painless lactation | |
| J. E. | i | 21 | 1 c.c. | Painless lactation | |
| J. W. | i | 22 | 1 c.c. | Painless lactation. | Excellent |
| C. H. | iii | 23 | 1 c.c. | Painless lactation | |
| B. Y. | i | 21 | 1 c.c. | Painless lactation. | Good |
| W. F. | i | 21 | 1 c.c. | Painless lactation. | Good |
| M. J. | i | 17 | 1 c.c. | Painless lactation | |
| I. S. | i | 29 | 1 c.c. | Painless lactation | |
| J. B. | ii | 29 | 1 c.c. | Painless lactation | |
| J. B. | ii | 31 | 1 c.c. | Painless lactation | Pain 48 hours post partum for 10 hours |
| D. B. | ii | 22 | 1 c.c. | Painless lactation | |
| C. D. | ii | 28 | 1 c.c.* | Poor | |
| A. W. | ii | 30 | 1 c.c. | Painless lactation | |
| M. S. | i | 21 | 1 c.c. | Painless lactation | |
| C. B. | v | 24 | 1 c.c. | Painless lactation | |

*Plus 1 c.c. 3 days later.

*Testosterone propionate, 20 mg., plus estradiol benzoate, 1 mg. per cubic centimeter, supplied as Gynetone Injection, through the courtesy of Schering corporation, Bloomfield, N. J.

the other, the result was poor even with a repeat injection of 1 c.c. on the fourth postpartum day.

There was no diminution of milk secretion in any case. No nursing difficulties were encountered (Table I).

Of 33 patients in whom lactation was inhibited, excellent results occurred in 9 and good results occurred in 19. Results were fair in 4. One of these patients received a 1 c.c. dose; after 2 days of lactation, a second dose of 1 c.c. Gynetone was administered and lactation ceased 48 hours later. Results were poor in one case (3 per cent). Successful results occurred in 97 per cent (Table II).

TABLE II. SUPPRESSION OF LACTATION WITH COMBINED ANDROGEN-ESTROGEN THERAPY

| PATIENT | GRAVIDA | AGE (YEARS) | DOSAGE | LACTATION* | RESULTS |
|---|---|---|---|---|---|
| J. P. | iv | 30 | 2 c.c. | ++ | Good |
| G. Q. | v | 41 | 2 c.c. | ++ | Good |
| M. K. | iv | 28 | 2 c.c. | + | Excellent |
| E. D. | iii | 30 | 2 c.c. | ++ | Excellent |
| M. T. | iii | 26 | 2 c.c. | ++ | Good |
| J. D. | vi | 31 | 2 c.c. | ++ | Good |
| H. D. | vi | 39 | 2 c.c. | ++ | Good |
| J. B. | iv | 26 | 2 c.c. | +++ | Fair |
| H. S. | v | 29 | 2 c.c. | ++ | Good |
| R. S. | ii | 21 | 2 c.c. | ++ | Good |
| J. H. | v | 38 | 2 c.c. | ++ | Good |
| M. W. | ii | 30 | 2 c.c. | ++ | Good |
| W. W. | i | 20 | 2 c.c. | + | Excellent |
| R. C. | i | 39 | 2 c.c. | +++ | Good |
| S. S. | i | 35 | 2 c.c. | ++++ | Fair† |
| W. R. | v | 33 | 2 c.c. | ++ | Good |
| W. W. | i | 21 | 2 c.c. | ++ | Good |
| C. U. | i | 26 | 2 c.c. | + | Excellent |
| C. M. | i | 31 | 2 c.c. | ++ | Good |
| G. K. | i | 21 | 2 c.c. | ++++ | Fair† |
| M. S. | i | 17 | 2 c.c. | ++++ | Poor |
| A. B. | i | 20 | 2 c.c. | ++ | Good |
| L. M. | i | 28 | 2 c.c. | ++ | Good |
| W. M. | ii | 25 | 2 c.c. | + | Excellent |
| L. W. | i | 25 | 2 c.c. | + | Excellent |
| R. S. | ii | 22 | 2 c.c. | +++ | Good |
| J. S. | i | 19 | 2 c.c. | ++++ | Fair |
| W. M. | ii | 28 | 2 c.c. | + | Excellent |
| R. N. | v | 28 | 2 c.c. | ++ | Good |
| J. C. | ii | 22 | 2 c.c. | ++ | Excellent |
| M. N. | ii | 23 | 2 c.c. | ++ | Good |
| B. B. | ii | 29 | 2 c.c. | + | Excellent |
| F. I. | ii | 26 | 2 c.c. | ++ | Good |

*Lactation stopped in:
+—1 day
++—2 days
+++—3 days
++++—4 days
†1 c.c. first 24 hours.
1 c.c. after 2 days' lactation. Lactation ceased 48 hours later.

Of 12 patients who had in previous pregnancies received stilbestrol, all preferred the present androgen-estrogen combination therapy. Many had previously suffered nausea from stilbestrol.

In the present series, there were no instances of nausea, vomiting, fever, malaise, urticaria, or any of the other side effects reported as having occurred with estrogenic therapy. There were no increased bleeding tendencies, nor did any patient complain of engorged breasts, either during treatment or upon withdrawal of medication.

## Summary

Painless lactation in 88 per cent of patients resulted from a 1 c.c. intramuscular dosage of androgen-estrogen combination (testosterone propionate, 20 mg., plus estradiol benzoate, 1 mg. per cubic centimeter) during the first 24 hours post partum.

Inhibition of lactation in 97 per cent of patients resulted from a single 2 c.c. intramuscular dose of this same androgen-estrogen combination.

No side actions were observed.

No supportive therapy or other measures of any kind were employed.

It is concluded that in the prevention of lactation and painful postpartum breast engorgement an androgen-estrogen combination (testosterone propionate, 20 mg., plus estradiol benzoate, 1 mg. per cubic centimeter as Gynetone injection) offers therapeutic advantages as well as greater convenience to both patient and physician.

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# A METHOD FOR THE DETECTION OF RUPTURED MEMBRANES THROUGH EXAMINATION OF VAGINAL CYTOLOGY

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*(From the Dade County Cancer Institute)*

VARIOUS investigators have occupied themselves with the problem of how to determine whether or not the membranes are ruptured. They can be divided into two groups. The first group searches for products of the fetus or the membranes, such as hairs, fat droplets, products of the vernix caseosa, or enveloping membranes. The second group investigates the hydrogen-ion concentration of the vaginal contents. The alkaline amniotic fluid makes the vaginal contents, normally acid, more or less alkaline, and one might determine according to the reaction whether or not the membranes are ruptured. As an indicator, litmus paper, bromthymol blue, or the nitrazine reagent is used. The change takes place with a pH of 6 to 6.5. Apart from this relatively large scope of variation, it is obvious that blood, vaginal secretions, alkaline or acid urine, antiseptic solutions, etc., can bring about such great changes that the reaction becomes impure, while a slight flow of liquor amnii, which, moreover, may have ceased some time ago, cannot bring about a change in the pH permanently. For that reason, the investigations of the first group are more exact; at least if the criterion occurs regularly. We regret that this cannot be said of the investigation for membranes and hairs, while the investigation for fat droplets is not sufficiently specific. Hairs are very specific and have certain characteristics described minutely by Philipp.[3] Microscopically they should show the following characteristics: (1) they should have little pigment; (2) they should be smooth and, in places, show epithelial scales; (3) they should not be bent or folded; (4) they should have a sharp, tapering point.

In preparations in which they occur, these characteristics are so specific that they can be clearly distinguished from artificial products, fibers, etc. With ruptured membranes, however, they occur so rarely that for one patient a great number of preparations are necessary to find one hair, so that the method requires too much time and trouble. Other methods consist of the evidence of fat drops in the vernix caseosa made visible by the coloration technique with sudan III.[2] The investigation for the epithelial cells of the vernix caseosa gives very good results. Bourgeois[1] was the first to describe the method. Vernix caseosa is formed from the sixth lunar month of gestation, but Bourgeois states that it is found constantly only at the beginning of the ninth lunar month. The fetal epithelial cells, as they occur in the vernix caseosa, are made up of translucent, polygonal, anucleate cells, although in

places nuclear remnants are still visible as uncolored residue. The protoplasm is slightly granular and furrowed by a network of fine little canals which communicate with one another. Occasionally there is degeneration of the protoplasm, visible in the protoplasm as droplets (fatty degeneration or nuclear degeneration?). The whole is translucent, appears as a shadow, and with the Papanicolaou stain assumes very light colors, mostly light green, gray-white, pink, sometimes light brown. Occasionally the epithelial cells are folded and crinkled, now lying together in groups, now simple. The differentiation from vaginal epithelium is very clear, since vaginal epithelium appears much more compact and distinct. The vaginal cells have been recently desquamated and are much more deeply colored, both as regards the protoplasm and the nucleus. The cells of the vernix caseosa, however, appear only as anucleate shadows.

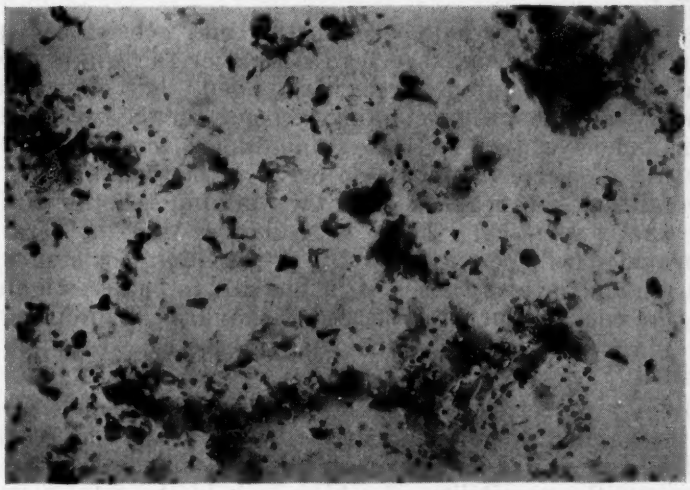


Fig. 1.—Vaginal mucus containing vernix caseosa and vaginal epithelium.

The vaginal epithelium, although less translucent, also appears in all shapes and colors and has a granulated structure. Moreover, vaginal epithelial cells may also rarely lose their nuclei, especially under the influence of vaginal bacteria. If one takes into consideration, moreover, that, owing to blood, fibrin, leukocytes, and mucus, the whole preparation often becomes an obscure mass even if spread thinly, it is evident that in practice this investigation is not easy. These difficulties increase owing to the various staining reactions of the cells, not only through the differences in pH of the vagina, but also because a staining method such as that of Papanicolaou, where several coloring agents are used, can never be applied without slight, involuntary changes being made in the time of staining, decolorizing, washing in alcohol, etc. Therefore we have found it necessary to modify the Bourgeois method, to make its use more practical.

## Method

The preparation is divided into two parts and epithelium from the vernix caseosa of a child is placed in advance on one half. This is fixed and kept in

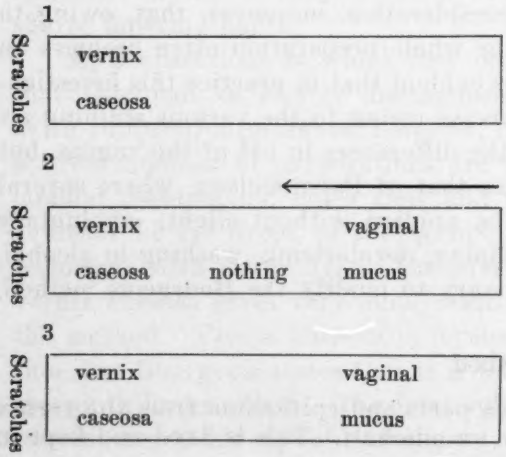
a bottle with equal parts of 96 per cent alcohol and ether. When it is necessary to investigate a case for ruptured membranes, the preparation is taken from the alcohol-ether solution, the unused half carefully wiped clean and dry, this half is checked microscopically to make certain that it does not contain vernix caseosa epithelium and a thin layer of vaginal mucus is then spread on this half.

The preparation is now stained and the two halves can be compared immediately. In this way the slide is divided into three parts:

1. The vernix caseosa, of which epithelial cells are clearly recognizable by their typical characteristics and which now, under the influence of the specific staining, have assumed a specific structure and color.
2. The part between 1 and 3 on which nothing is visible.
3. The part on which the vaginal mucus has been spread and on which the epithelial cells of the vernix, if present, can be recognized quickly and easily, as identical with those of the first part since they have been stained in the same way.

Another method is perhaps even better and consists of spreading the vaginal mucus, starting from the clean side, over the whole preparation, including the vernix epithelium already provided. An objection to the first method may be that, though the staining response for the two halves has become the same, this is not yet true for the vaginal mucus, since its pH may be basic, acid, or neutral. A perfect comparison between the two halves is possible only when the conditions, as regards both the staining reaction and the pH reaction, are exactly identical. There is no danger that the vernix epithelium originally provided will be wiped off the preparation, for a sufficient number of cells will remain for comparison with the half to be investigated. In order to facilitate the comparison, little scratches should be made in advance on the edge of the glass slide which has the vernix caseosa, so that it can later be easily identified.

Glass slides with vernix epithelium are stored in alcohol-ether in order to investigate the vaginal mucus when an occasion arises. The results have been entirely satisfactory so far and have agreed with the clinical facts. There remains, of course, the possibility of a high leak in the fetal membrane, when according to the microscopic investigation the membranes are ruptured and yet seem to be clinically intact since the bag of waters is present and the membranes are ruptured later and liquor amnii flows off. This would make it appear as if the investigation of the vaginal mucus has not been correct.




1. The slide in alcohol-ether solution.

2. The same slide with a thin layer of vaginal mucus spread on one half in the direction of the arrow.

3. Vaginal mucus spread on the whole slide.

It is clear that in this third case the vaginal mucus must be spread on the glass slide only once, otherwise mucus from the vernix would be placed on the half of the preparation on which vaginal mucus has been spread.

In the second case, left is compared with right and the staining reactions are identical. In the third case, left is compared with right and not only the staining reactions but also the pH reaction are identical.

The procedure is quick and simple. When the membranes are ruptured, this is often apparent at a glance. When they are intact the investigation naturally is more prolonged in order to make a positive diagnosis. The result is not influenced by vaginal secretions or antiseptics.

The vaginal smear is best made by exposing the portio and taking the smear as near the cervical os as possible. In that way the vernix caseosa cells are most easily found because there they are in greatest concentration.

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# THE LE FORT OPERATION*

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WHEN we see an elderly woman suffering from a complete or partial genital prolapse, we should not overlook the possibilities of relief from the relatively simple Le Fort operation. For various reasons, such as extreme age (ranging from 55 to 84 years in this series), complicating factors like diabetes, hypertension, obesity, cardiovascular disease, and senility, or the failure of previous operative attempts to correct the condition, both the family and friends may shy away from the idea of operating upon such an elderly woman. On the other hand, the family and physician have usually exhausted their patience with palliative measures, such as pessaries, etc., and beg to have something done. In the light of the foregoing, it seemed timely to present this subject anew.

The Le Fort operation is not a new or original procedure, although it is subject to many variations and modifications, depending on the experience and ingenuity of the operator. Adair and DaSef, in their presentation in 1936, gave an exhaustive historical background, dating from the first suggestion of such an operation in 1823 by Gérardin, up to 1876, when Le Fort popularized the operation bearing his name. Much of this material was culled from journals now inaccessible and makes interesting reading. From 1900 to 1925 there are only occasional reports. Recent articles appearing in the literature include those by Phaneuf[1] in 1935, by Adair[2] in 1936, by Tauber[3] in 1947, and by Mazer and Israel[4] in 1948, all reporting relatively small series. Indeed, from 1867 to 1930, only 230 cases were reported. By the same token, this group is small, including only fourteen cases from 1944 to 1951. It is now only 120 years since Gérardin's first report.

Phaneuf[1] states that "palliative measures may give relief—only surgery is curative." I might add that palliative measures give some relief but not for long. There are several good reasons for selecting the Le Fort operation.

In the first place, it might be stated that the Le Fort operation is a relatively simple procedure, for the following reasons:

A. Minimal operative risk
B. Minimal danger of embolism
C. Minimal anesthesia (may be done under local)
D. Minimal danger of thrombophlebitis
E. Minimal danger of infection
F. No shock or hemorrhage
G. No trauma to pelvic viscera
H. Low or no mortality or morbidity
I. Ideal suitability for debilitated elderly women with hypertension, diabetes, obesity, myocardial damage, or those who are otherwise poor operative risks.

*Presented at a meeting of the Pittsburgh Obstetrical and Gynecological Society, Feb. 4, 1952.

Second, these women, in our series, with two exceptions, were very aged women who sought relief for prolapse from which they had suffered from one to twenty years. Nine of the fourteen had exhausted their patience or the possibilities of relief by palliative measures.

A third consideration was the gratifying results obtained, as reported by others, and as exemplified in this small group. The patients' appreciation of the results justify the procedure. A few of their statements, to be given later, will illustrate this.

It is necessary to consider some of the prerequisites for the Le Fort operation.

It must be understood that this operation precludes marital relations. As is most frequently the case, eleven of these women were widows. The others, after explanation, readily consented to this stipulation.

The cervix and uterus must both be free of cancer. The experience of many gynecologists has shown that if cancerous lesions are absent at this age, they are quite unlikely to develop later. Curettage and biopsy were performed in all cases where the uterus and cervix were present.

This operation should be reserved for elderly women, who, because of their general physical condition, are unsuited to other types of surgical procedures, such as combined vaginal repair and laparotomy, vaginal interposition, vaginal hysterectomy, high vaginal fixation, Manchester-Fothergill procedure, and/or such other procedures or combination of procedures as are within the capacity of the operator.

As a final prerequisite, in my opinion, there should be reasonable outlook for a number of years—three to five or more—of ambulant, fairly active life. Naturally a patient who is bedridden or likely to be moribund within a few months is not to be considered.

I would like to review briefly, in Table I, some of the anamnestic and clinical data of this group, as well as some of the accompanying symptoms, in addition to prolapse, for which they sought relief.

TABLE I

| | |
|---|---|
| Average age | 71½ years |
| Widow | 11 cases |
| Still married | 3 cases |
| All had children (average 3½) | 2-7 cases |
| Hypertension | 9 cases |
| Diabetes | 2 cases |
| Senility | 3 cases |
| Previous operation | 9 cases |
| Previous operation for prolapse | 6 cases |
| Bowel symptoms | 2 cases |
| Incontinence | 5 cases |
| Difficulty in voiding | 6 cases |
| Incomplete emptying of bladder | 1 case |
| Leg pains | 3 cases |
| Nonprotein nitrogen | 30-42 cases |
| Previous pessary treatment | 9 cases |

The duration of the prolapse varied from nine months to twenty years; the time consumed in operation was from thirty-five to sixty minutes; patients were permitted out of bed from the eighth to the thirteenth postoperative day.

In some instances where a large cystocele only was present the Le Fort operation was the simplest solution.

It has been stated that a large part of the operation can be done without anesthesia. That has not been our experience, since it has been difficult to maintain many of these elderly women in the lithotomy position without some de-

gree of anesthesia and relaxation. Several of them were too apprehensive and one too agitated for us to work with any facility without anesthesia. For the most part, a small amount of Pentothol, supplemented by nitrous oxide and oxygen, was sufficient. On the other hand, one patient, on whom a light nitrous oxide-oxygen anesthesia was started, tolerated it poorly before the beginning of the operation. The anesthesia was discontinued and the operation finished without additional anesthesia.

Two features of the preoperative and postoperative care should be emphasized. First, thorough preoperative evacuation of the lower bowel should be assured. In one case, there was a fecal impaction postoperatively and, in the struggle to relieve this, we fear some of the suture lines were loosened, resulting in a small cystocele. We always employ a Foley catheter with continuous drainage, insuring an empty bladder at all times. The amount and rapidity with which the bladder fills varies in different individuals. With a routine order to empty it every 4 to 6 hours, we may find anywhere from 200 to 1,200 cm. of urine distending the bladder.

All but one patient reported for a follow-up examination. Of the thirteen who reported, a good-to-excellent anatomical result was obtained in twelve, and a fairly satisfactory anatomical result in one. The functional disturbance of the bladder varied from inability to void when the prolapse was down, to a stress incontinence. The functional result was good in ten, fair in one, no change in two, and apparently unsatisfactory in one as reported by letter. This last patient was a highly agitated widow with many home and financial difficulties which seemed to keep her in a turmoil. Leg pains were relieved in one, improved in one, and unrelieved in a third. There were no mortalities.

## Summary

We have presented our experience with the Le Fort operation in the treatment of genital prolapse in fourteen elderly women whose ages ranged from 55 to 84 years. The varieties of prolapse included that of the uterus with cystocele and/or rectocele, prolapse of the vagina, and large cystocele or rectocele alone. These women, because of their age, hypertension, diabetes, obesity, or senility, were unsuited to more extensive surgical procedures. They all met certain prerequisites outlined. The results in this series justify our recommending to such individuals, that, in preference to prolonged trial with pessaries, they can best be served by the Le Fort operation, which entails minimal operative risk and postoperative complications.

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# CLINICAL EVALUATION OF SULFONAMIDES IN CERVICAL AND VAGINAL THERAPY

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A CLINICAL evaluation of the efficacy of sulfonamides in various combinations was undertaken in a variety of gynecological conditions. The sulfonamide preparation eventually selected for evaluation consisted of a combination of sulfathiazole 3.42 per cent, N′ acetylsulfanilamide 2.86 per cent, N′ benzoylsulfanilamide 3.7 per cent, and urea peroxide 1 per cent in a jelly (cream) base.*

## Material

The patients in this study included 110 with cervicitis with and without cervical erosion and Nabothian cysts, 3 with cervical polyps, 19 with cervical erosion for whom a biopsy was done, and 71 patients with vaginitis of varying etiology. This group represents only those who were followed for sufficient time to determine the outcome of treatment.

The group of 110 patients with cervical inflammation ranged in age from 22 to 54 years and all but 4 were married; 89 had one or more children.

TABLE I. SOCIAL GROUP

| | NUMBER OF CASES | AGE (YEARS) | MARRIED | SINGLE | CHILDREN | | |
|---|---|---|---|---|---|---|---|
| | | | | | NONE | ONE | MORE |
| Cauterization | 95 | 22-49 | 93 | 2 | 15 | 19 | 61 |
| Coagulation | 8 | 23-54 | 6 | 2 | 5 | 1 | 2 |
| Conization | 7 | 31-49 | 7 | 0 | 1 | 0 | 6 |
| Cervical polyp | 3 | 27-48 | 2 | 1 | 2 | 1 | 0 |
| Cervical biopsy | 19 | 25-57 | 18 | 1 | 3 | 3 | 13 |
| Vaginitis | 71 | 20-76 | 67 | 4 | 22 | 10 | 39 |

The chief complaint was vaginal discharge and pain in the lower pelvis or back. All of these were treated by either cervical cauterization, coagulation, or conization.

TABLE II. SYMPTOMS

| | MENSTRUATION | | DISCHARGE | | | PAIN | | |
|---|---|---|---|---|---|---|---|---|
| | REG. | IRREG. | SLIGHT | MODERATE | PROFUSE | NONE | BACK | LOWER QUADRANT |
| Cauterization | 70 | 25 | 17 | 17 | 23 | 20 | 54 | 57 |
| Coagulation | 7 | 1 | 2 | 0 | 2 | 1 | 5 | 3 |
| Conization | 7 | 0 | 2 | 0 | 2 | 1 | 5 | 4 |
| Cervical polyp | 3 | 0 | 0 | 1 | 0 | 1 | 2 | 1 |
| Cervical biopsy | 14 | 5 | 3 | 4 | 4 | 2 | 15 | 13 |
| Vaginitis | 29 | 42 | 13 | 16 | 20 | 21 | 43 | 27 |

*Commercially known as Triple Sulfa Cream. Supplied by the Medical Research Division, Ortho Pharmaceutical Corporation.

The day following one of these electrophysical procedures the patient was instructed to use Triple Sulfa Cream in the following manner: A plastic vaginal applicator of 5 c.c. capacity was filled by screwing the end onto the screw tip of the tube of cream. By pressure on the base of the tube the plunger of the applicator was displaced until the barrel was filled. The barrel was disconnected from the tube and the tip of the applicator inserted between the labia into the vagina for about one inch. The plunger was then depressed depositing the contents within the vagina. This was repeated every night. No douching was permitted. These patients were seen every other day for the first two weeks and once a week thereafter until the local area was healed. At each of these visits the vagina was cleansed and a cotton-tipped applicator saturated in Mercurochrome was introduced into the cervical canal. The average time for complete healing to occur was 5 to 6 weeks. The details appear in the accompanying table.

TABLE III. TIME REQUIRED FOR CURE

| | CAUTERIZATION | COAGULATION | CONIZATION | POLYP | BIOPSY | VAGINITIS |
|---|---|---|---|---|---|---|
| Average | 5-6 weeks | 6 weeks | 5 weeks | 4 weeks | 4 weeks | 3-4 weeks |
| Shortest | 2 weeks | 10 days | 2 weeks | 2 weeks | 1 week | 1 week |
| Longest | 16 weeks | 8 weeks | 7 weeks | 12 weeks | 10 weeks | 16 months |
| Unimproved | 1 case | 0 | 1 case | 0 | 2 cases | 22 cases |

A comparison with a former series of patients of similar type and with similar pathology treated by the same electrophysical modalities shows that the time required for cure was appreciably shortened in this present group. In the previous group the average time required for cure was four months.[1] The healing progressed smoothly. In no instance was there any malodorous discharge and the tissues maintained a clean appearance after the initial slough was cast off.

The cervical polyps were treated by removal with a high frequency cutting current. The 19 biopsies were done with the high frequency cutting loop. After therapy, sulfonamide cream was applied as previously described. In these patients healing took place in an average of four weeks.

Vaginitis, in the group of 71 patients with this diagnosis, was due to a variety of causes. Among these were Trichomonas, fungus, diabetic, menopausal, postmenopausal, and senile vaginitis and a number of cases of undetermined origin. Treatment in this group consisted in the daily application of Triple Sulfa Cream until a decision could be reached as to its effects. The inflammatory changes and symptoms disappeared in 49 of these patients in an average of three to four weeks of treatment. The other 22 cases showed no improvement. The details are indicated in Table IV.

TABLE IV. VAGINITIS, 71 CASES

| | CURED | IMPROVED | UNIMPROVED |
|---|---|---|---|
| Trichomonas | 24 | 5 | 9 |
| Pruritus vulvae | 0 | 1 | 1 |
| Diabetic | 0 | 1 | 0 |
| Menopausal | 1 | 1 | 1 |
| Postmenopausal | 1 | 4 | 4 |
| Senile | 0 | 2 | 1 |
| Atrophic | 0 | 1 | 0 |
| Fungus | 0 | 0 | 1 |
| Leukoplakia | 0 | 0 | 1 |
| Undetermined | 2 | 6 | 4 |

## Reaction

Two patients complained of discomfort and itching following the use of sulfonamide cream for several days. Examination showed redness and edema of the labia. Medication was discontinued and the reaction subsided within 48 hours in each case.

## Summary and Conclusions

Two hundred three patients were treated with Triple Sulfa Cream and were followed until the results of treatment could be determined. One hundred ten treated for cervicitis with electrophysical modalities healed more rapidly and with no complications when Triple Sulfa Cream was the only postoperative medication used. The 71 patients with vaginitis responded to the extent of improvement in the inflammatory reaction. In the patients with trichomoniasis, the improvement probably was a result of the elimination of concomitant bacterial agents rather than the destruction of the trichomonads. Very little local sensitivity to this sulfonamide combination was noted.

These results conclusively indicate that the use of Triple Sulfa Cream is a valuable adjunct in electrophysical therapy of cervical infection, as well as in the treatment of local vaginal inflammatory processes.

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151 West 77th Street

# THE USE OF THE MALE NORTH AMERICAN TOAD (BUFO AMERICANUS) IN THE DIAGNOSIS OF PREGNANCY*

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IN THE United States the common leopard frog (*Rana pipiens*) was introduced for biological pregnancy testing by Robbins and Parker (1948).[1] In a controlled series of 122 tested urine specimens no false positive reactions occurred, and only one false negative reaction was encountered on a urine sample obtained early in the period of gestation.

The reliability of the North American male frog (*Rana pipiens*) was summarized in 1949 by Robbins and Parker.[2] Three hundred routine diagnostic specimens were injected, resulting in an over-all accuracy of 96 per cent. Most of the false negatives were encountered in cases of normal pregnancy within the first month of amenorrhea. One false positive was encountered in the urine of a patient with intense obstructive jaundice. Other samples similar to the one described resulted in false positive reactions. Although the ultimate basis for the false positive reaction was obscure, it was emphasized that the repetition of incorrect results can be avoided by rejection of all icteric urine specimens. The frog test failed to achieve the accuracy of the immature rat in the Aschheim-Zondek test. In competent hands the Aschheim-Zondek test reveals an accuracy of approximately 99 per cent, compared to 96 per cent accuracy in the Robbins and Parker series. Many advantages of the use of the frog test tend to outweigh the small difference of sensitivity.

Seasonal variation in sensitivity of the *Rana pipiens* to chorionic gonadotropin was soon recognized as a great disadvantage. Samson[3] reported 11.2 per cent of the frogs refractory in a summer series of 1,376 diagnostic tests. The animal is quite sensitive to the chorionic gonadotropin during the fall, winter, and early spring months. Only 0.5 per cent of the frogs were refractory during these three seasons. During the cooler seasons the frog would react to between 2 and 5 I.U. of the hormone. As the animal is relatively insensitive during the summer, an increase to 10 to 25 I.U. of gonadotropin is necessary for the stimulation of spermatogenesis. Brody[4] and others have reported the necessity of using concentrates prepared from large amounts of urine to produce accurate results. The basis of the Aschheim-Zondek, Friedman, and amphibian tests is the level of chorionic gonadotropin; the animals with less seasonal variation and with greater sensitivity for the early pregnancy levels produce the more consistent accuracy.

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## Method

In this series the common male garden toad (*Bufo americanus*) was used as the diagnostic animal. The garden toad can easily be found in the areas east of the Rocky Mountains, north to the Hudson Bay and south to the Gulf of Mexico. Because of the wide distribution the toads are easily obtainable locally or from biological supply houses.

The male toad can be easily differentiated from the female. The presence of a croak and dark pigmentation of the skin over the throat is characteristic of the male. The female is never audible, and the skin of its throat is white or slight brown. One cannot, however, determine the sex by the clasping digit as in the differentiation of the *Rana pipiens*.[5] Also, the female toad is usually larger and has a rougher skin than the male.

This series consists of 268 tests. One hundred thirty-five of the diagnostic urine specimens were submitted for an Aschheim-Zondek test. Also, fifty-two of the specimens were injected into the male frog (*Rana pipiens*).

The method used requires no special training. The test consists essentially of the injection of freshly voided urine into the dorsal lymph sac of the toad. The test specimen can be collected at any time during the day, although most of the diagnostic samples were from the first morning micturition. If the samples are not used immediately, they are kept in a refrigerator. A relatively small volume of urine is necessary, as concentration methods are not used. Medication and diet have no effect on the test results. The urine is injected into the dorsal lymph sac without concentration, filtration, pH adjustment, or any other previous preparation.

As the toads are to be reinjected for diagnostic tests at weekly intervals, the amount of urine injected each time is kept at a minimum. When 2.5 c.c. or 3.0 c.c. of urine are injected, identical results occurred as when 5.0 c.c. or more are used. A 22 gauge needle is introduced through the skin in the posterior mid-thigh region for the injection. With the needle just beneath the skin it is pushed along toward the midline where the dorsal lymph sac is located just beneath the skin in the caudad back region. Careless or deep injections may result in puncturing the lungs which the toad inflates when handled. The toads are placed in individual containers until the time for examination of the cloacal contents.

Procurement of the urine from the toad is a simple matter. It is obtained by introducing a small glass pipette into the cloaca. Gentle movements of the pipette result in a small amount of urine collecting in the pipette by capillary attraction. The sample is placed directly on a glass slide and without staining is observed under low power of a microscope with reduced illumination. If the test is positive, many spermatozoa are present. The number of spermatozoa is insignificant as the urine dilution of the toad is variable. The spermatozoa are hairlike and motile. If they are observed under high power, they are noted to have a head, a long thin tail, and a shorter threadlike flagellum.

The urine from the toads is observed at two hours, at three hours, and the day after injection. Eighty-three per cent of the positive reactions are positive in two hours. One hundred per cent of the positive samples are positive reactors at the three-hour reading period. Spermatozoa in the positive reactors may continue to be found positive for twenty-four to thirty-six hours.

After the third positive weekly injection in the same toad the reaction would usually occur after the two-hour observation. No uniform delay occurs, as a great variation is noted in the reacting time of different toads. Repeated use of the toad may be made at intervals of one week for six to eight tests without decreased accuracy.

Some of the urine samples proved to be toxic, either killing or making the toad very sick. Detoxification is performed by shaking the urine with an equal amount of ether. Decantation and filtration of the urine completes the procedure.

In the project the toads were divided into two groups. Group I was kept in a box with compartments containing soil and a small tray of water. Six compartments made it possible to keep the toads separated for their weekly rest periods. The hardy toad usually burrows and could be kept at ordinary room temperature without danger of excessive drying as occurs in frogs. Group II was kept in small, individual specimen containers which were kept in the laboratory refrigerator at approximately 38° F. As the toad is a cold-blooded animal, a state of hibernation was induced resulting in the lowest metabolic activity. The toads were placed on moist paper in the containers which eliminated keeping a tray of water present. As the toad is noiseless in hibernation and imparts no odor, the containers may be placed in any office refrigerator. Under the conditions of Group II, the animals are kept in better condition and for a longer period than animals in Group I. Before injection the toads were allowed to remain at room temperature for one or two hours. Feeding is not required in either group if the animals are kept for ten to twelve weeks.

This series of 268 tests was divided into the following two groups:

Group I. Two hundred eight tests were performed on toads at room temperature.

Group II. Sixty tests were performed on toads kept in a refrigerator at 38° F.

In Group I, 119 tests were positive, and the remaining 89 tests were negative. All of these results were checked by the Aschheim-Zondek test and/or by irrefutable clinical evidence of pregnancy. In no case did a nonpregnant urine sample give a positive result. Results agreed in all but 5 cases. In 4 of these tests the toad gave a negative result while the Aschheim-Zondek test was positive. These 4 patients were proved clinically to be pregnant. In one case the toad test was positive and the Aschheim-Zondek was negative. This patient was proved to be pregnant clinically, and at a later date the Aschheim-Zondek became positive. In 52 of these assays the *Rana pipiens* test resulted in eight negative reactions, and in the comparative series the toad test resulted in two false negative reactions. In Group I, the toad test was 97.6 per cent accurate in 208 trials. In 135 tests the Aschheim-Zondek was 99 per cent accurate, while in 52 cases the *Rana pipiens* resulted in 84 per cent accuracy.

In Group II, 49 positive and 11 negative reactions occurred. Again no false positive reactions were encountered. One false negative result occurred in a total of 50 patients who were clinically pregnant, and the remaining 10 samples were from nonpregnant subjects. In this group the accuracy was 98.3 per cent.

The reliability of the toad test was similar to that given in other reports,[2, 7] in which the male frog (*Rana pipiens*) and the Batrachia, respectively, were used for test animals. Accuracy of the *Rana pipiens* in this series was comparatively lower (84 per cent) than in the reported series; but these tests were performed during the late spring and summer when the hibernation levels of the *Rana pipiens* are less stable. Inaccuracy in this series was not related significantly to the trimester of pregnancy. Investigators[6] have reported that chorionic gonadotropin falls to a low level in the third trimester, but no false negative reactions occurred in the last trimester of pregnancy.

In other large series, accuracy obtained by using the South American toad (*Bufo arenarum* Hensel),[8] the *Bufo woodhousii*,[5] and the *Rana pipiens*[2] for diagnostic animals varied from 96 to 99 per cent. On a theoretical basis the variation between the toad test and other tests resulting in from 96 to 99 per

cent accuracy is totally obscure. In all cases the results depend upon the reaction to gonadotropic hormone of a test animal which may develop disorders of the normal physiological function.

This toad test possesses the qualities desired in an ideal biological pregnancy test. The test is simple, since no special training is necessary to perform the procedure, no surgery is necessary before results can be observed, and the time consumed for injection and later reading is approximately two minutes. One hundred per cent of the results can be obtained in three hours. The urine specimens from pregnant women or from women with hydatidiform moles or chorionepithelioma result in a specific positive reaction. The toad can be used in all seasons without fluctuations in accuracy. The end point is definite as spermatozoa are present only when a positive urine is injected and is absent in other conditions. The toad can be reinjected six to eight times without decrease in accuracy if a rest period of one week is allowed between injections. The method of refrigeration in small containers lends itself to adaptation as an office procedure. By this method one dozen animals could be used for seventy-two or more diagnostic tests. Toads are inexpensive and can be purchased for two to three dollars per dozen in most areas. Six cents per test was the average cost for each test performed in this series. Feeding, handling, or other special care is not necessary if the animal is used for ten to twelve weeks and then replaced by a new animal. This analysis indicates the common toad (*Bufo americanus*) possesses certain advantages over other test animals.

## Summary and Conclusions

1. A series of diagnostic tests demonstrates that the common toad (*Bufo americanus*) reacts excellently to chorionic gonadotropin.

2. Two hundred sixty-eight tests were performed with an over-all accuracy of 97.9 per cent.

3. No false positive reactions occurred in 100 negative urine samples. There were 5 false negative tests in 168 positive urine samples.

4. One negative Aschheim-Zondek test was proved incorrect first by the toad test, then by clinical evidence, and by a later Aschheim-Zondek test.

5. Fifty-two tests on the *Rana pipiens* during the late spring and summer months resulted in lower accuracy (84 per cent) than the toad tests in the same season. Seasonal stability and continued hibernation in captivity are definite advantages of the toad when compared with other amphibian test animals.

6. A simple method of refrigeration makes the toad an easily accessible and practical test animal.

7. The toad test is a simple, rapid, and economical biological pregnancy test which presents advantages as an office procedure.

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# USE OF THE MALE GRASS FROG (RANA PIPIENS) IN PREGNANCY TESTING

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SINCE the original articles of Wiltberger and Miller[1] and Robbins and Parker[2] on the use of the male frog, *Rana pipiens,* in tests for pregnancy, numerous reports have appeared in the literature describing experience with this test. In the original articles, it appeared that the test was in the order of 99 per cent accuracy, with rare false negative and no false positive tests, but further experience revealed that occasional false negative and false positive results could be expected. The latter are especially frequent in urine from jaundiced patients, Sobel and Edelman[3] reporting positive tests in 9 of 21 jaundiced nonpregnant patients. Soucy[4] first reported a high percentage of false negative reactions in the summer months and Holyoke[5] showed that more than eight times as much chorionic gonadotropin is required in July, August, and September to produce a positive test than is necessary in the other months of the year.

## Material

The frog pregnancy test has been in use at this hospital for the past two years, 207 tests having been performed. The technique as described by Cutler[6] was followed, using urine concentrated by Scott's method, but with the final volume of solution reduced so that 1 ml. contained the hormone from 30 ml. of urine. Two frogs were employed routinely, the first being injected with 1 ml. and examined at the end of 30 minutes. If no spermatozoa had been discharged, a second frog was injected with 2 ml. and both animals observed over a two-hour period unless spermatozoa appeared sooner. Positive animals were not reused. Negative animals were autopsied to confirm the presence of gonads. Histologic study of the testes revealed no significant difference in the various months of the year; spermatozoa were seen in the tubules in about the usual numbers in the frogs which gave false negative tests in the summer of 1950.

## Results

Results of this study are shown in Table I. All tests included were followed up after three months or later, when the clinical status of the patient was unquestionable. Over 80 per cent of tests were performed on urine from patients whose last menstrual period was less than three months previously. The false positive reactions were scattered throughout the period of study, in patients who ranged in age from 19 to 35 years, and who were all within three months of the last normal menstrual period; none of them was jaundiced. Three false positives occurred in frogs which had been given the equivalent of 60 ml. of urine, while the paired frog receiving 30 ml. equivalent did not react. The other three positives occurred with the 30 ml. equivalent doses. In one of the latter cases, immediate surgery showed a large parovarian cyst

with no evidence of pregnancy and a repeat frog test five days later was negative. Whether or not the other two false positives may have been clinically unrecognized early abortions could not be determined. All but two of the false negative results occurred in the summer of 1950 when *Rana pipiens* frogs were used; sixteen tests performed in the summer of 1951 using *Rana clamitans* yielded no false negative reactions and in each case the frog reacted to a dose of 30 ml. equivalent of urine. This is in accord with the experience of Reinhart, Caplan, and Shinowara,[7] who found that in the summer months *Rana clamitans* was about eight times as sensitive to their "gonadotrophic powder" as *Rana pipiens.*

TABLE I

| | TRUE NEGATIVE | TRUE POSITIVE | FALSE NEGATIVE | FALSE POSITIVE |
|---|---|---|---|---|
| Number of tests | 78 | 108 | 15 | 6 |
| Percentage | 93 | 88 | 12 | 7 |

## Summary

In 207 tests over two consecutive years, the male frog pregnancy test has shown 90 per cent over-all accuracy. Negative results secured with *Rana pipiens* during the summer months are not reliable; the use of *Rana clamitans* at this time appears to obviate this difficulty. False positive reactions in one-half the cases appeared to be due to use of too large a dose of urine equivalent.

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# ESTRONE SULFATE SOLUBLE IN THE TREATMENT OF ESTROGEN DEFICIENCY

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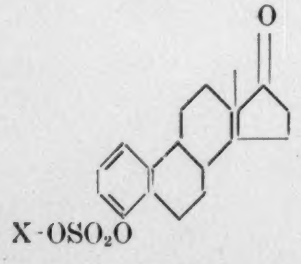
WITH the demonstration by Zondek[1] in 1930 that pregnant mare's urine is rich in a diversity of active and inactive steroids, it was not long before this plentiful source was tapped for clinical use. The most abundant of the active estrogens found in pregnant mare's urine is a soluble sulfate of estrone,[2] commonly referred to as "estrone sulfate." This fraction of pregnant mare's urine is used loosely to identify estrogenic concentrates derived from such a source, although pregnant mare's urine contains an unknown proportion of this conjugate and sundry other water soluble sulfates of inactive steroids.

It is the practice of some to standardize estrogenic concentrates of pregnant mare's urine in terms of "estrone sulfate" and to refer to such extracts as though specific quantities of estrone were actually present. This is calibrated as the result of fluorometric studies and bioassay, and as much of the pregnant mare's urine extract is put into each dose as will correspond to these quantities. Refinements in concentration of pregnant mare's urine, beyond that which is feasible on a commercial plane, have failed to give a pure product. These difficulties in the preparation of pregnant mare's urine and the inability to produce uniform dosages in tablets made from such material have led to conflicting reports as to absolute estrogenic potency when used in treatment of conditions characterized by estrogen deficiency.[3-10]

It is evident that good therapy is based on accurate dosage of crystalline pure, physiologically active drugs. Actually, pure estrone sulfate soluble has been known since 1939.[11] This report concerns its initial clinical assay.

Chemically, estrone sulfate soluble is the water soluble conjugate of estrone and a selective cation X as shown in the structural formula. Butenandt[11] produced it by conjugating pure estrone and obtaining pure sodium estrone sulfate. This material has a molecular weight of 388, melting point of 228-230° C., optical rotation $[a]^{20} = 1 \div 110$; with one mole of water of crystallization; the compound is stable below its melting point and occurs in the form of colorless needles.



## Material

Estrone sulfate soluble, in the crystalline pure form, was assayed clinically, using tablets of 1.25 mg. administered orally in the treatment of the menopause and primary and secondary amenorrhea. This material was used in the treatment of one hundred patients, as follows:

Fifty patients suffering the symptoms of natural menopause were treated with estrone sulfate soluble. These patients were divided into three categories: (1) severe, having 8 to 20 flushes a day; (2) moderate, 4 to 10 flushes a day; (3) mild, 2 to 4 flushes a day.

Patients in the severe category were treated as follows:

All patients were started on a regime of estrogenic therapy by intramuscular injection, using 1.3 mg. estradiol benzoate, twice weekly for six weeks; then 1.3 mg. estradiol benzoate once weekly for three weeks; followed by 0.3 mg. estradiol benzoate once weekly for three weeks, and thence by oral administration estrone sulfate soluble, 1.25 mg. daily. Seventeen patients in this group (68 per cent) were well maintained on oral therapy. Eight patients (32 per cent) could not be maintained on the tablets; it was necessary to revert to intramuscular injections of estradiol benzoate. There were five patients classified as having moderate menopausal symptoms (4 to 10 flushes a day). This group was treated with 1.25 mg. oral estrone sulfate soluble twice daily. Only one patient was relieved of symptoms following this regime. In four patients the flushes were not controlled with the dosage as outlined.

Twenty patients having mild menopausal symptoms (2 to 4 flushes per day) were treated with one tablet of 1.25 mg. estrone sulfate soluble daily. Menopausal symptoms were eliminated in all patients in this group and the frequency of the dose was reduced after two months of treatment.

Twenty-five patients were treated with estrone sulfate soluble following hysterectomy and bilateral salpingo-oophorectomy. Treatment in all patients was started on the first day postoperatively. Therapy consisted of one tablet of 1.25 mg. estrone sulfate soluble twice daily for one month, gradually reduced to one tablet every two or three days. None of the patients so treated ever developed any menopausal symptoms.

In the amenorrheic group treated there were twenty-five young women between the ages 15 to 21 years. These cases were about evenly divided between primary and secondary amenorrhea. Therapy was cyclic in character and consisted of two tablets of 1.25 mg. estrone sulfate soluble daily for twenty days followed by injections of 10 mg. progresterone intramuscularly for five days. In all instances bleeding occurred. The therapy was given for an initial course of three months. Sixteen patients in this group have continued to menstruate regularly following cessation of treatment.

The nine patients remaining were given another course of treatment as outlined above for an additional three months. At the end of that time three patients continued menstruating. The remaining six patients are still under observation.

## Summary

1. Estrone sulfate soluble is a potent oral estrogen free of untoward side effects. None of the patients treated suffered nausea, vomiting, or any other disagreeable side action as a result of treatment with this material.

2. Estrone sulfate soluble is a crystalline pure estrogenic hormone; consequently, the clinical effectiveness of this material as an estrogen and the dosage requirements can be accurately evaluated.

3. It produced completely estrogenic vaginal smears in all cases.

The crystalline pure estrone sulfate soluble used in these studies was kindly supplied by the Schering Corporation, Bloomfield, N. J.

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# THE STORAGE OF ESTROGEN IN HUMAN FAT AFTER ESTROGEN ADMINISTRATION*†

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RECENTLY at the meeting of the House of Representatives' Committee to investigate the use of chemicals in food products,[1] the question was brought up whether the administration of estrogen-like substances in the hormonizing of chickens resulted in storage of these hormones in the fat. Are administered estrogens stored in the fat? The question needs to be answered. In the fowl and in cattle it may have decided drawbacks, for if there is storage it means that those who ingest this food will also be receiving estrogenic substances. The ingestion of such food stuffs, it was felt, is tantamount to administration of estrogens to children, men, and women. This problem needs clarification since so much hormonal caponization and hormonization of cattle are being performed today.

The question arises concerning the storage of estrogenic substances in human fat. There is very little in the literature to afford an answer to this question.

## Material

The Department of Endocrinology at the Medical College of Georgia undertook this study to ascertain if estrogenic substances are stored in subcutaneous fat of human beings. Eleven normal women who were scheduled for laparotomy for various reasons were given natural and synthetic estrogens by the various routes of administration—orally, parenterally, and by pellet implantation—prior to operation. Subcutaneous fat samples were obtained in the course of the operation and immediately placed in a 50-50 mixture of benzene and alcohol. The entire sample of fat, including the benzene-alcohol mixture, was placed in a Waring blender, macerated, and then filtered through cheese cloth. This macerated fat was blended and extracted twice again to insure complete extraction, and then the filtrate was evaporated to dryness over steam. The oily residue was then suspended in olive oil for assay. This material was injected at various dose levels into immature mice and the mouse uterine weight method of Evans, Varney, and Koch[2] was employed for the assay of estrogens. Results were calculated in Tace units per 100 Gm. of fat, and 1.7 $\mu$g. of Tace is equal to one mouse unit.

Previous studies on rats, comparing the synthetic estrogen Tri-p-anisyl-chloroethylene (Tace) and hexestrol,[3] showed that there was no retention of estrogenic substances in the fatty tissues following hexestrol but there was retention following Tace. Fig. 1 illustrates the results in rats. A single dose, 15 mg. of Tace and 7.5 mg. of hexestrol, was administered to respective groups of rats. Biopsies of fat were obtained on the first, fifth, and tenth days. The

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fat assay from the control and hexestrol groups of rats failed to elicit any estrogenic activity, while the group receiving Tace showed marked storage in the fat and a slow release of estrogenic substances over a relatively long period.[4]

In our study in human beings, we extended the investigation to additional natural and synthetic estrogens. We have tried to find evidence of fat storage of estrogenic substances with estrone, estradiol, and stilbestrol.

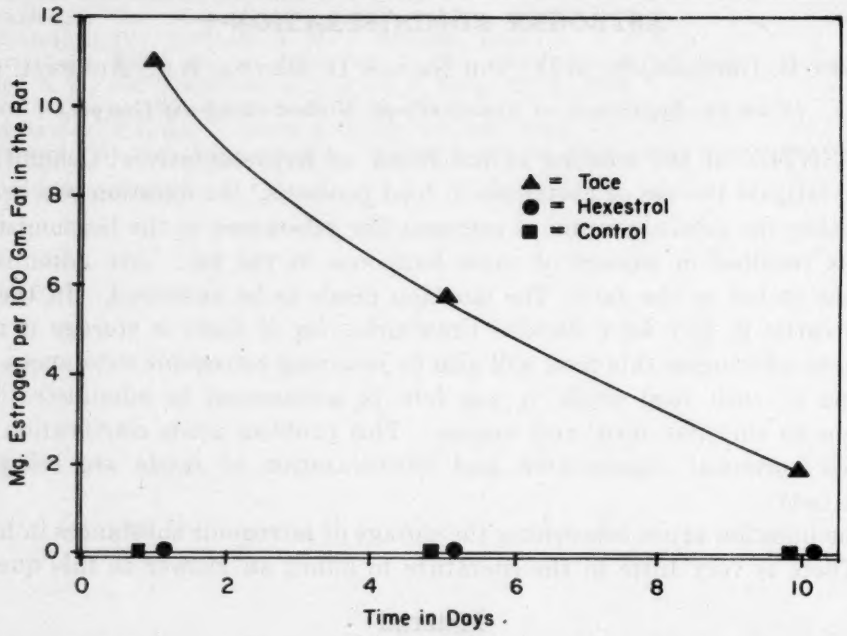


Fig. 1.—Courtesy of Research Laboratories, The Wm. S. Merrell Company, Cincinnati, Ohio. Unpublished data.

## Results

Table I shows the results obtained in this study. Four subjects were used as controls, receiving no estrogenic substances. No estrogenic activity was found in the fat of the control subjects.

Three subjects were given various natural estrogens. Two subjects from this group were given estrone only, while the remaining subject received 75 mg. of estradiol in pellet form in addition to estrone. These estrogens were given over varying periods of time and the subject who received the pellets was naturally under constant estradiol stimulation. Both subjects who received only estrone and were biopsied 12 and 20 hours, respectively, after the last dose, showed a very faint trace of estrogenic activity per 100 Gm. of fat obtained. This activity was so slight that it could not feasibly be expressed in numerical terms. It suffices to say that only a faint trace could be noted.

The subject who received estrone plus the pellets of estradiol showed no estrogenic activity in the fat biopsied.

Four subjects were given Tace orally in doses ranging from a total of 504 to 1,152 mg. in periods varying from 3½ to 16 days. Fat biopsies were obtained from 10 to 60 hours after the last dose of Tace. All four subjects showed marked estrogenic activity per 100 Gm. of biopsied fat. It is of interest to note that there is evidently a saturation point reached with respect to the fat storage of Tace. All four subjects show striking similarity in the amount of estrogenic activity per 100 Gm. of fat. All of the subjects apparently show estrogenic

storage of 0.420 (± 0.06) mg. of Tace per 100 Gm. of fat. Further studies are now in progress to ascertain the minimum dosage necessary to bring about a fat storage concentration of the above figure.

For academic interest we assayed fat from a chicken commercially caponized with stilbestrol. The fat sample showed no traces of estrogenic activity. This may seem of little interest, but when one realizes that a comparable dose in a 60 kilogram woman would be equivalent to around 1,800 mg. on a kilogram for kilogram basis, it becomes rather significant.

TABLE I. ESTROGEN ACTIVITY OF HUMAN FAT AFTER SYNTHETIC AND NATURAL ESTROGEN ADMINISTRATION

| NAME | TACE (MG.) | OTHER ESTROGENS (MG.) | SCHEDULE OF TREATMENT | TIME LAPSE FROM LAST DOSE TO BIOPSY | ACTIVITY IN MG. OF TACE/100 GM. FAT |
|---|---|---|---|---|---|
| Estes | 0 | 0 | CONTROLS | — | 0 |
| Pope | 0 | 0 | | — | 0 |
| Rutledge | 0 | 0 | | — | 0 |
| Scott | 0 | 0 | | — | 0 |
| Edmundson | 0 | 90 mg. estrone sulfate I. M. | Given over 10 day period | 12 hours | Faint trace |
| No. 6 | 0 | 2 mg. estrone I. M.<br>75 mg. pellets estradiol | Estrone and estradiol Pellets given 30 days prior to biopsy | →→→→→→→ | 0 |
| Crosley | 0 | 30 mg. estrone | Given over 3 day period | 20 hours | Faint trace |
| Woodward | 1152 mg. | 0 | 2 t.i.d. for 16 days | 60 hours | 0.424 mg. |
| No. 4 | 504 mg. | 0 | 3 q.i.d. for 3½ days | 15 hours | 0.402 mg. |
| Johnson | 1008 mg. | 0 | 2 t.i.d. for 14 days | 10 hours | 0.485 mg. |
| Swords | 1152 mg. | 0 | 2 t.i.d. for 16 days | 15 hours | 0.370 mg. |
| Chicken fat | 0 | 2-15 mg. stilbestrol pellets | 1 pellet 30 days before biopsy<br>1 pellet 15 days before biopsy | →→→→→→→ | 0 |

## Conclusion

It has been previously shown in studies in rats that, following the administration of Tace and other synthetic estrogens such as hexestrol and diethylstilbestrol, significant amounts of estrogenic material were recovered from rats receiving Tace while none was found in rats which received hexestrol. A comparative study of estrogen deposition in the subcutaneous fat was made in normal women serving as controls and in women following the administration of Tace and other estrogens. Preliminary studies indicate that estrogen storage in subcutaneous fat is pronounced following administration of Tace but not after other estrogens employed in this study. This depot storage of estrogen may be of clinical and therapeutic significance.

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# Department of Case Reports New Instruments, Etc.

## HIDRADENOMA OF THE VULVA*

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*(From the Presbyterian Hospital)*

WE DESIRE to present three cases of hidradenoma of the vulva. This lesion is a small, infrequent, usually asymptomatic, almost always benign tumor arising from the large apocrine sweat glands of the vulva. The clinical importance of this tumor lies primarily in the fact that microscopically it is not infrequently mistaken for an adenocarcinoma and the patient subjected to needless surgery[1] or irradiation.

Hidradenoma of the vulva most frequently presents, clinically, as a 1 to 2 cm. sharply circumscribed skin lesion that has the appearance and consistency of a sebaceous cyst, but may be firm and resemble a fibroma.[2] The overlying skin is usually intact but may ulcerate. When ulceration occurs, pain, bleeding, and pruritus may be complained of. The lesion is most frequently located on the labia majora, but may be found anywhere on the hair-bearing area of the perineum.[2]

The microscopic appearance is quite characteristic, the general architecture being that of innumerable acini and tubules separated by delicate connective tissue,[4] with irregular papillary projections into cystic spaces.[1] The epithelium lining the tubules and covering the papillary projections is two layered,[4] thus being characteristic of the apocrine glands from which the tumor arises.[1] There is an inner layer of large columnar or cuboidal cells and an outer layer of spindle-shaped myoepithelial cells that rest on a thin basement membrane.[3] Mitotic figures are rarely seen, there is little anaplasia, and no evidence of local invasion.

CASE 1.—A 40-year-old white woman, at the time of vaginal hysterectomy in 1946, was found to have a pea-sized cystic tumor of the right labium majus. This lesion was completely excised at the time of surgery and the microscopic report was adenomatous polyp. The slides were reviewed at a later date and revealed the typical picture of a hidradenoma.

CASE 2.—A 50-year-old white woman with a past history of a vaginal hysterectomy in 1947 consulted her physician in 1949 because of an asymptomatic swelling of the right labium majus noticed for the first time three weeks previously. Examination revealed a 1 cm. cystic tumor. The lesion was completely excised and microscopically presented the picture of a hidradenoma.

CASE 3.—A 50-year-old white woman with a past history of a vaginal hysterectomy in 1947 consulted her physician in 1950 because of a painful tender mass of the left labium majus. Examination revealed a 1-cm. cystic mass of the upper portion of the left labium majus with ulceration of the overlying skin. The lesion was completely excised and microscopically was found to be hidradenoma.

All the cases reported in the literature as well as our three cases, with the exception of one case reported by Eichenberg,[5] were cured by simple excision. This one case was possibly not a hidradenoma, but rather a primary adenocarcinoma or the recently reported Paget's disease of apocrine gland origin. However, despite this almost 100 per cent cure by simple excision, it is advisable to keep the patient under observaton for a reasonable period of time.

*Presented before the Chicago Gynecological Society, May 18. 1951.

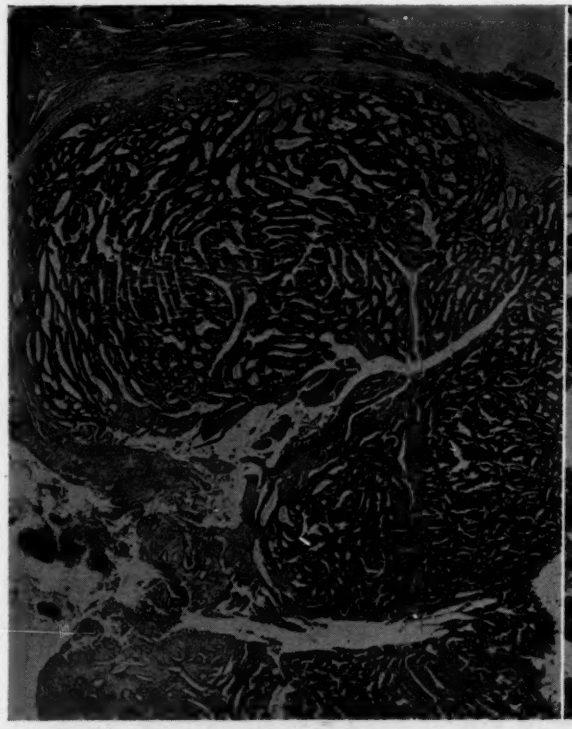

Fig. 1.

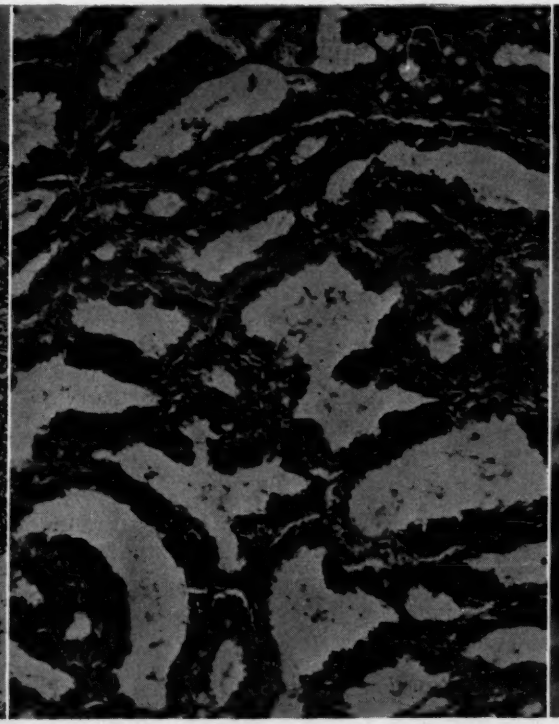

Fig. 2.

Fig. 3.

Fig. 1.—Low-power photomicrograph from the lesion described in Case 3, showing the highly adenomatous structure of the tumor. Note that the lesion is well circumscribed and surrounded by a fibrous tissue capsule. Also ulceration through the overlying epidermis can be seen.

Fig. 2.—A higher power photomicrograph showing more clearly the adenomatous structure, the irregular papillary projections into cystic spaces, and the two-layered epithelium.

Fig. 3.—A still higher power photomicrograph showing distinctly the two-layered epithelium.

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55 East Washington Street

# SARCOMA OF THE ROUND LIGAMENT*

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TUMORS of the round ligament of the uterus are uncommon. The first recorded case was described by Virchow[1] as a yellowish mass removed in 1805 by Walter from the round ligament of a 37-year-old woman. Virchow believed it to be a myoma. Many years later Wells[2] reported two cases of inguinal tumors which were described as "fibrous tumors of the round ligament." One was the size of a large orange, in a 40-year-old woman; the other the size of a coconut, in a woman aged 50 years. The first review of tumors of the round ligament was published in 1883 by Sanger.[3] He found 11 cases of tumor of the round ligament and added one of his own, a fibrosarcoma. His was the first case of a sarcoma of the round ligament recorded. Cullen[4] described the first case of adenomyoma of the round ligament in 1895. Emanuel[5] in 1903 collected 76 cases and added 4 of his own. The next review to appear was in 1914 by Taussig.[6] He found 61 more cases, including his case of a spindle-cell sarcoma, bringing the total number of cases of round ligament tumors to 141. In 1933 Watkins[7] collected 32 additional reports. Of the 173 cases reported, Watkins was able to classify 167 of them as follows: 87 fibromyomas (approximately 50 per cent were associated with fibromyomas of the uterus); 47 adenomyomas or endometriosis, which like fibromyomas were frequently associated with endometriosis of other pelvic structures; 24 cystic tumors, including 3 dermoid cysts; 8 sarcomas, 2 additional cases having been reported since Taussig's review (in all but one, the sarcoma represented a malignant degeneration of a fibromatous growth); and 1 lipoma, occurring in a newborn infant as a bilateral tumor.

During the same year, Horine[8] reported a collection of 36 cases since Taussig's review. Of his series, 5 of them were sarcomas (2 fibrosarcomas, 2 sarcomas, and 1 fibromyosarcoma). Two of these were the same cases of sarcoma reported by Watkins, so that there was a total of 11 sarcomas of the round ligament reported by that time.

Since 1933, a number of tumors of the round ligament have been described. They included the first 2 cases of hemangioma of the round ligament; one of them resembling a strangulated inguinal hernia. Only 4 additional cases of sarcoma of the round ligament were reported, two of these by Novak,[9] a spindle-cell sarcoma of the round ligament. The case we are reporting at this time, as well as we can determine, makes a total of 16 sarcomas of the round ligament.

## Case Report

The patient, S. T., is a white woman, aged 35 years, gravida iv, para ii. The onset of her menses was at 14 years. Periods were every 28 days with a duration of 5 days and were not associated with pain. The past medical history revealed only a history of a trolley accident in March, 1948, with injury to the leg. In 1942, she had an abortion of a female fetus at the twenty-fourth week of pregnancy. In 1944, she was delivered of a living male child at term by low forceps and right mediolateral episiotomy. A second abortion in 1948 occurred at the same stage of pregnancy as the first; this was also a female child. She was again delivered of a living male child at term by low forceps and right mediolateral episiotomy on June 6, 1950.

On Oct. 6, 1950, a small nodule, the size of a pea, was noticed at the upper part of the right labium majus toward the groin. This was not painful. There was no evidence

*Presented at a meeting of the Philadelphia Obstetrical Society, Nov. 1, 1951.

of infiltration and the skin was freely movable over the growth. On Jan. 6, 1951, the patient was examined and the area where this nodule was first noticed was enlarged, and had spread upward and somewhat laterally so that its size now was about that of an English walnut. The area appeared purplish in color, somewhat fixed, but not painful or tender. It was firm in consistency and somewhat irregular. The patient volunteered that this enlargement occurred over a period of 10 days to 2 weeks.

She was hospitalized on Jan. 15, 1951. Temperature, pulse, respiration, blood pressure, and blood count were normal. Urinalysis revealed a trace of albumin and 20 to 30 white blood cells per high-power field. The sedimentation rate was 10 mm. in 2 hours. Wassermann and Kahn tests were negative. X-ray of the chest was essentially negative.

Fig. 1.—Shows the deep surface of the original tumor. The mass measures 3.5 by 3.4 by 2 cm. It is irregular in outline, gray, and firm.

On Jan. 17, 1951, the mass was biopsied and a frozen section performed. It was a fibrosarcoma. The frozen section of subcutaneous fat beneath the superficial tumor also showed the neoplasm. A radical procedure was performed the following day after the patient had received 500 c.c. of whole blood. The anesthetic was nitrous oxide, oxygen, and ether. Tissue removed was bounded by a line extending from the right anterior superior spine of the ilium, across the abdomen to a point 4 mm. beyond the midline on the left side, downward to the base of the right labium and laterally to the right anterior superior spine. This area, including the labium majus, was removed en masse, the depth reaching to the fascia and including the external portion of the round ligament with its terminal portion in the large labia. As the dissection was progressing, a knob was found in the region where the tumor originated. When this knob was mobilized and an attempt at resection started, traction outward revealed the true origin of the growth. It was noticed that the round ligament with its vessel was being pulled through the inguinal canal. The ligament was resected after a piece of considerable size was exposed. The stump and vessel were ligated, transfixed, and attached by suture to prevent retraction. All vessels were ligated and the wound closed with interrupted silk sutures.

The original specimen (Fig. 1) consisted of a firm, fleshy, gray, glistening, subcutaneous nodule measuring 3.5 by 3.4 by 2 cm. The surface was covered by an elliptical piece of skin. The normal skin markings were obliterated over the lesion.

Histologically (Fig. 2) the sections consisted of a portion of skin containing a large infiltrating neoplasm replacing the lower two-thirds of the collagen and subcutaneous tissue. The epidermis was intact and appeared regular. The hair shafts and sebaceous glands were acutely angulated because of the underlying tumor. The sweat glands were dilated. The neoplasm was a solid, cellular sheet of rather uniform spindle cells. These cells were arranged in cords and a whorled pattern running in different planes. The nuclei were spindle shaped, hyperchromatic, and varied considerably in size. Approxi-

mately one mitosis was found per high-power field. Under low power, there was a suggestion of palisading of the nuclei. The cytoplasm was amphophilic. The vessels were not a prominent feature of the tumor. Other sections (Fig. 3) revealed that the tumor extended deeply into the subcutaneous tissue. The neoplasm took a pale green color with the Mallory's trichrome stain. The diagnosis was a fibrosarcoma of skin, well differentiated, with extension into adjacent subcutaneous tissue.

Fig. 2.—Consists of a portion of skin containing the infiltrating neoplasm. The tumor is composed of uniform spindle cells arranged in cords and whorls. (×50.)

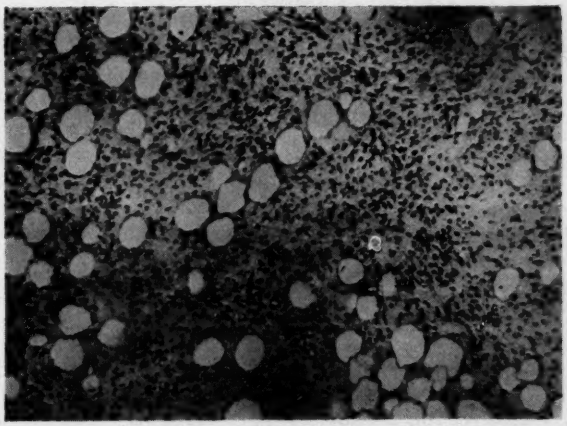

Fig. 3.—Shows the involvement of the subcutaneous tissue by the tumor. The same uniformity of cellular pattern is evident. Mitoses are common. (×100.)

The specimen removed at the time of the second operation consisted of three portions, including skin and two separate portions of soft tissue. The skin measured 12.2 by 3 by 1.4 cm. with attached soft tissue weighing 14 Gm. The soft tissue included several pieces, the larger measuring 3.6 by 2.8 by 1.4 cm. It was composed mostly of yellow, gray, friable, fatty tissue. Cut section revealed a firm, tan, central area. Histologically, the sections revealed skin and subcutaneous tissue containing remnants of the original neoplasm. The section taken at the periphery of the specimen did not contain tumor.

Following operation, the patient received 500 c.c. of blood. She was out of bed the day following operation and left the hospital in good condition on the sixteenth postoperative day. The blood count was normal.

The patient has been observed at regular intervals. At the present time, she is feeling well and has been menstruating regularly. She is pursuing her household duties and living a normal sexual life.

*Comment.*—The round ligament runs through the entire inguinal canal and is inserted into the subcutaneous tissue of the labia majora and the pubic spine. The proximal two-thirds of the round ligament contains muscular tissue, but the distal third consists almost entirely of fibrous tissue.

The symptoms vary with the location of the tumor. They may be divided anatomically into intra- and extra-abdominal tumors. With the intra-abdominal type there may be no symptoms. But a large tumor may produce pressure symptoms involving the bladder, ureter, or bowel. The mass must be differentiated from uterine fibroids. Acute symptoms may result from a tumor on a twisted pedicle.

The extra-abdominal (canalicular or inguinal) type frequently resembles a hernia with a lump in the groin, pain, and pressure symptoms. In the labia majora, there may be a sense of heaviness or drawing. The pedicle of tumors in the labia majora extends from the inguinal canal through the external inguinal ring. The mass may grow to enormous size. A tumor reported by Craig weighed 30 pounds.

The intra-abdominal type is rarely diagnosed before operation, while the extra-abdominal type is often mistaken for a hernia or may actually be associated with a hernia. A hydrocele in the canal of Nuck may be confused with cystic tumors of the round ligament. The differential diagnosis here usually depends on finding tumor nodules in the canal. Endometrial tumors offer the best chance of diagnosis. The symptoms are more likely to be characteristic. Rapid growth of a previously existing tumor is the one indication of a sarcoma.

Surgical excision offers the best chance of a cure. Even with sarcoma, the prognosis is good with wide excision, providing the tumor is localized.

## Summary

A case of fibrosarcoma of the round ligament is reported with a review of the literature in which there were 15 cases previously reported. In the reported case, the patient was treated by radical excision of the tumor. She has been observed at regular intervals and at present is enjoying good health. The operative area is well healed with a good cosmetic result.

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255 South 17th Street

# ROENTGEN FETAL CEPHALOMETRY

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*(From the Midtown Hospital)*

A SATISFACTORY simple method of roentgen fetal cephalometry that has been in use for four years will be briefly described.

An adjustable upright is fixed to a turntable. At the top of the upright is a saddle-shaped piece of wood in which is sunk a metal ball (ball bearing) 4.455 cm. in diameter. The upright and the ball are on the axis of rotation (Fig. 1).

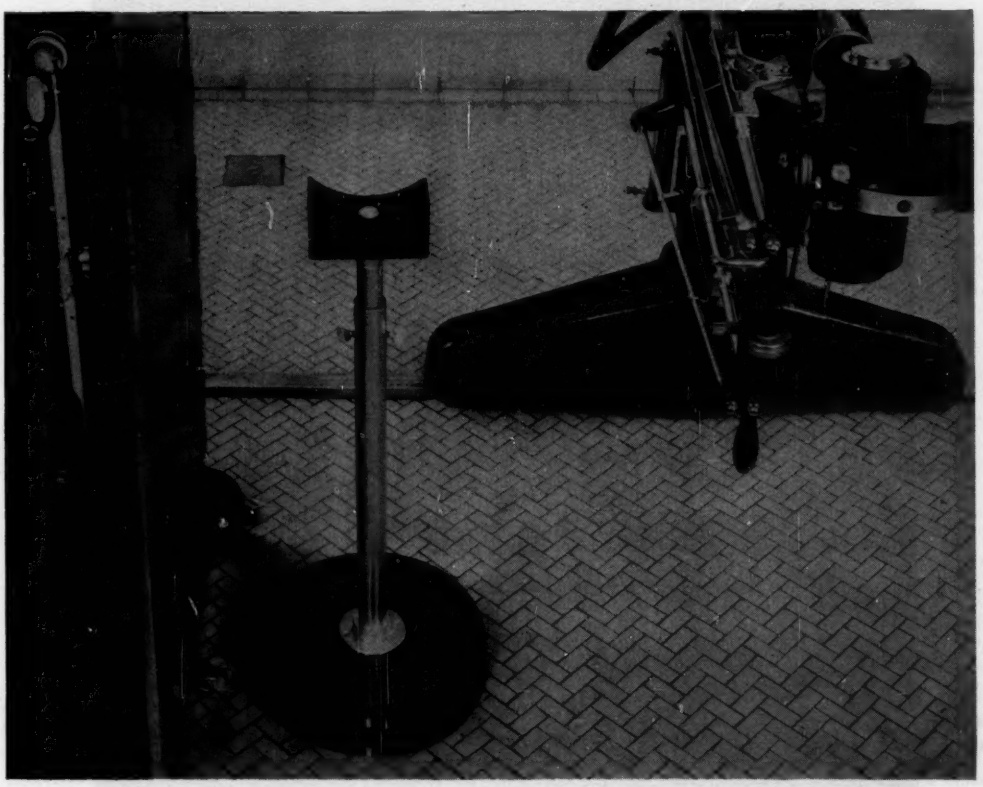

Fig. 1.

To determine a diameter of the skull the turntable is placed between the Potter-Bucky diaphragm and the roentgen tube, the turntable being as near the diaphragm as practicable. The tube is placed approximately on a level with the fetal head. The mother stands astride the upright with the thighs pressed firmly against the piece of wood, which is at the perineum. A film is exposed. The turntable and the mother are rotated together 180 degrees. A second film is exposed. The selected diameter of the skull and the horizontal diameter of the ball are measured on each film, the shadows of the ball being equal in

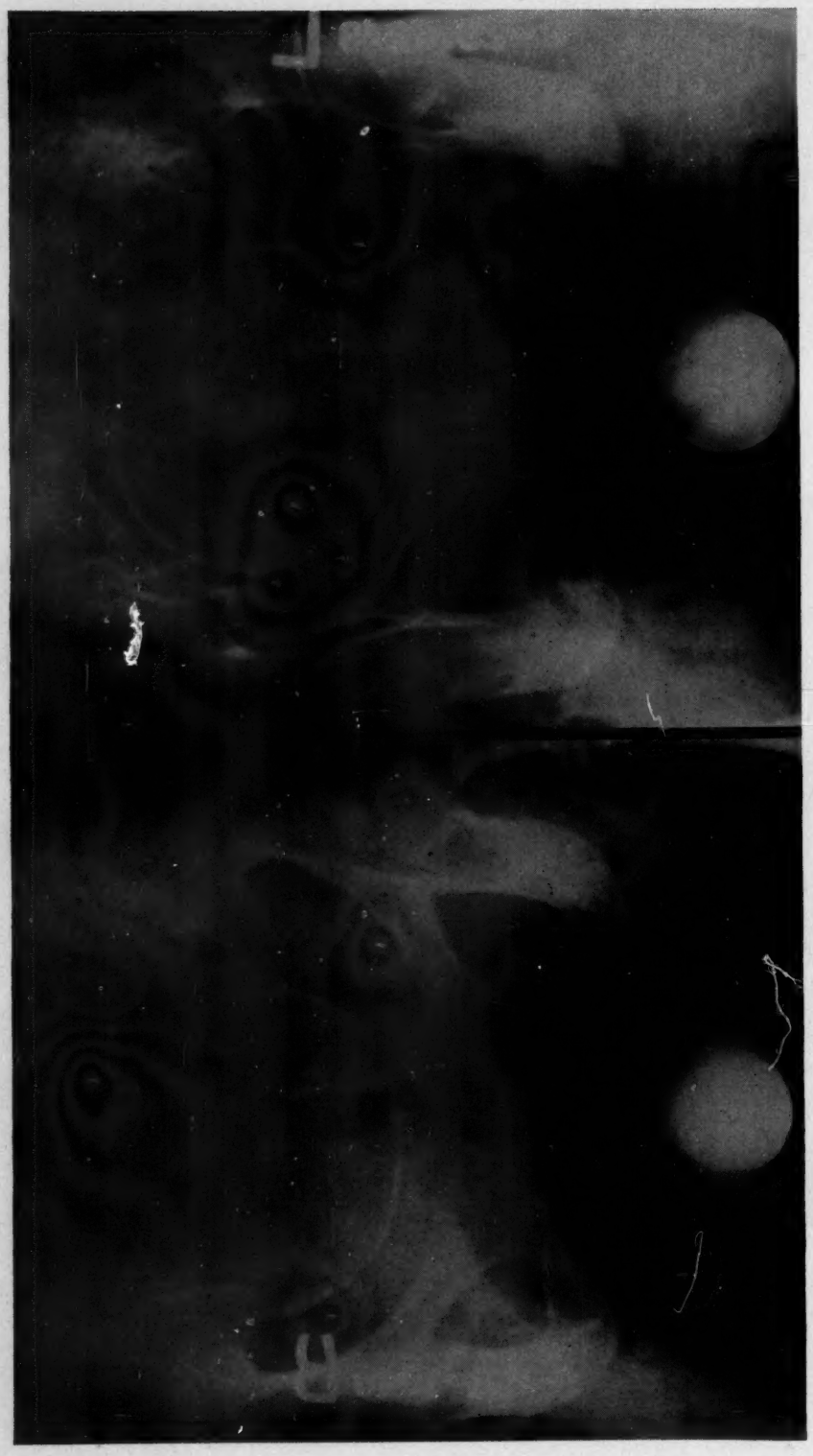

Fig. 2.

diameter (Fig. 2). A straightedge is placed on line AB in Fig. 3 at the point indicating the measured diameter of the skull on one film and on line EF at the point indicating the measured diameter of the skull on the other film. The point of intersection of the straightedge and the line CD indicates the calculated diameter of the shadow of the skull, the diameter that would have been measurable and equal on the films had the skull been on the axis of rotation. *Twice the product of the measurements on the films divided by the sum of the two equals the calculated diameter.* The straightedge is placed on line AB in Fig. 4 at the

Fig. 3

Fig. 4

point indicating the diameter of the ball (4.455 cm.) and on line CD at the point indicating the measured horizontal diameter of the shadow of the ball. The point of intersection of the straightedge and the line EF is noted. The straightedge is placed at the point just noted and on line CD at the point indicating the calculated diameter of the shadow of the skull. The point of intersection of the straightedge and line AB indicates in centimeters the selected diameter of the fetal skull. *The diameter of the ball divided by the horizontal diameter of its shadow equals the diameter of the skull divided by the calculated diameter of its shadow.*

121 East 60th Street

# A CATHETERIZING LARYNGOSCOPE* FOR TRACHEOBRONCHIAL ASPIRATION OF THE NEWBORN AND PREMATURE INFANT

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*(From the Department of Surgery, and the Department of Oto-rhino-laryngology, University of Rochester School of Medicine and Dentistry)*

EXTENSIVE experience in handling obstructive emergencies in the newborn infant has taught us actual bronchoscopy is seldom necessary.[1] As previously stated by the author,[2] such emergencies may be classified in three main groups: one, those where there is no actual obstruction but rather a central nervous system lesion and in which neither bronchoscopy nor tracheobronchial aspiration will be of value; two, those infants with obstruction due to aspirated mucus, meconium, blood, or vernix caseosa, and this is by far the largest group. It is in this group where immediate tracheobronchial aspiration may well be lifesaving. The third group is small and is made up of the few cases where bronchoscopy is necessary for the relief of actual correctable congenital anomalies. There were only two of the latter in the present series which has now reached a total figure of eighty-nine cases.

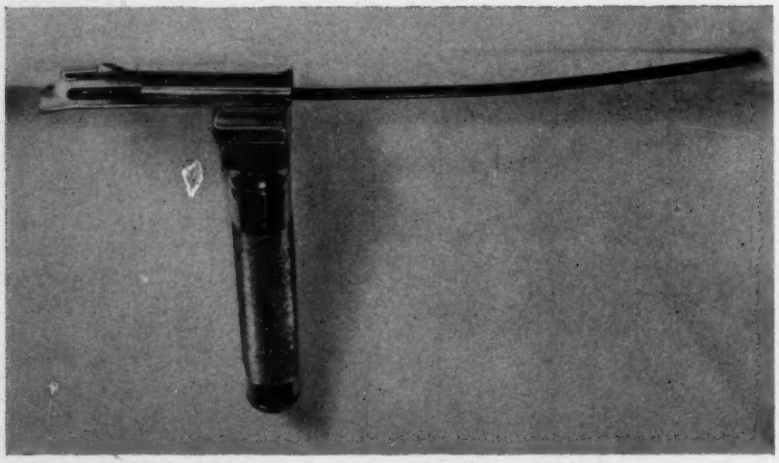

Fig. 1.—The catheterizing laryngoscope. A section of No. 11 ureteral catheter has been passed through the guiding tube.

In an effort to make available in the small hospital and the home a method of handling these emergencies, a technique of tracheobronchial aspiration has been described by the author.[2] In the course of time two problems made themselves evident when the instrumentation became part of the armamentarium of those not trained in endoscopy. One was that the laryngoscopes available were too large for easy manipulation especially in the premature infants. Two, the guidance of a catheter through or along the blade of the conventional laryngoscope presented to the operator not trained in endoscopy more of a technical problem than had been foreseen.

To make the tracheobronchial aspiration of the newborn and premature infant easier and less traumatic a new laryngoscope (Fig. 1) is being presented. It is new in two

*The catheterizing laryngoscope is available at the Foregger Company, Inc., 55 West 42nd Street, New York, N. Y.

respects: one, it is small enough to be more easily manipulated and less traumatic in use; two, it has built into the blade a guiding tube making insertion of the catheter into the tracheobronchial tree as nearly automatic as possible.

## The Instrument

To facilitate ease of transportation and handling, the light source has been incorporated into the handle, which holds pencil-light-sized batteries. This can be turned down parallel with the blade of the laryngoscope proper, reducing the bulk of the instrument to a minimum when in transportation or storage.

The blade of the laryngoscope has been shortened so as to conform with the size of the newborn infant's mouth, and is small enough to be adaptable to the mouth and throat of the salvageable premature infant with a minimum of trauma.

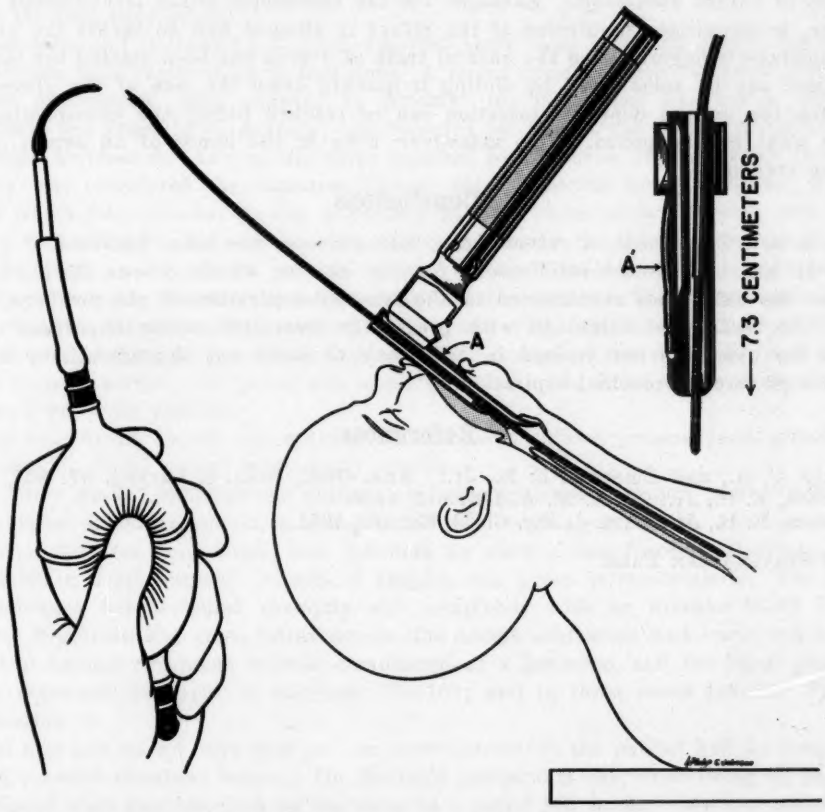


Fig. 2.—*A*, Schematic drawing illustrating the technique of tracheobronchial aspiration with the new catheterizing laryngoscope.

*A'*, A view of the bottom of the laryngoscope blade showing a catheter being passed through the guiding tube.

The suction apparatus has been previously described.[3]

Into the blade of the laryngoscope a tube has been fitted which acts as a carrier for the aspirating catheter. This tube accommodates a ureteral catheter up to size No. 11 French which experience has shown to be the upper limit of size which can be used repeatedly through the larynx of newborn and premature infants without undue trauma. This carrier is so placed that as soon as the cords come into view the operator merely has to advance the catheter through it to gain direct entrance to the larynx and tracheobronchial tree.

## Technique

The baby is held by an assistant with the head cradled in his hands in an extended position (Fig. 2). The laryngoscope is then inserted in such a manner as first to expose the uvula. Then the blade is tilted up enough so that the tongue is held up out of the way and the tip of the epiglottis can be seen. The next step is to drop the blade of the instrument just under the tip of the epiglottis and again raise the blade so that in the second position both tongue and epiglottis are held up and out of the way exposing the arytenoids and cords.

Once the cords are visualized the catheter is advanced via the catheter carrier and the entrance to the tracheobronchial tree is made, and aspiration carried out following a technique previously described by the author.[2, 3]

A trick of the trade that has been found useful and which tends to minimize trauma in the stronger or more resistant baby may be of value to those not well versed in the problems of infant endoscopy. Entrance for the endoscope, either laryngoscope or bronchoscope, is oftentimes facilitated if the infant is allowed first to suckle the gloved tip of the operator's finger. Once the natural train of events has been started the instrument to be used can be substituted by sliding it quickly down the side of the gloved finger, and often the desired depth of insertion can be reached before the unsuspecting infant realizes what has happened. This maneuver, even in the hands of an expert, tends to minimize trauma.

## Conclusions

1. A new instrument, a catheterizing laryngoscope, has been described.

2. It has been found satisfactory for the use for which is was designed, i.e., to minimize the difficulties encountered in the tracheal aspiration of the newborn.

3. The instrument combined with previously described suction apparatus makes it possible for operators not trained in endoscopy to carry out the oftentimes lifesaving procedure of tracheobronchial aspiration.

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26 Strathallan Park

# PREGNANCY COMPLICATED BY SUBARACHNOID HEMORRHAGE

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SUBARACHNOID hemorrhage as a complication of pregnancy, labor, or the puerperium is rare, although the condition has been established as a definite, relatively common clinical entity in the past sixty years.

Moskowitz and Schneider,[1] in 1938, reported three cases occurring during labor. They found thirteen cases reported up to that date. A recent review of the literature reveals nine additional occurrences. One reported by Stroink[2] in 1936 which involved a 33-year-old quartipara a few hours after delivery; one reported by Pancot and Galle,[3] secondary to an intracerebral accident due to syphilis; three reported by Dahle[4] in 1946, in which toxemia of pregnancy was considered the causative factor; three reported by Garber and Maier[5] in 1948, of which two occurred during pregnancy and the third after delivery; and one reported by Gershenfeld and Savel[6] in 1950 which occurred on the third postpartum day.

Mrs. M. M., a 23-year-old gravida i, para 0, was first seen at the eighth month of pregnancy after being followed in another part of the country. Family and past histories were irrelevant. Menarche had occurred at 13 years with periods of five days' duration, every twenty-eight days, with moderate flow and slight cramps at the onset. Physical examination was entirely normal; the pelvis was ample gynecoid. The Kahn test was negative. The blood was type O, Rh positive.

The antepartum course was entirely without note. Blood pressure and urinalysis remained normal. Total weight gain was 31 pounds.

At forty weeks' gestation the patient went into spontaneous labor. After twelve hours of labor under spinal anesthesia, a living male child weighing 9 pounds, 4 ounces, with the cord around the neck four times, was delivered by elective low forceps (DeWees), with a right mediolateral episiotomy. Pitocin, 1 ampule, was given intramuscularly. The placenta and membranes were expelled promptly and completely with an average blood loss. An ampule of Ergotrate was given intravenously, the uterus contracted and responded normally. The patient became somewhat restless, complained of a headache, and the blood pressure at the time registered 190/120; in one hour 150/100; and in three hours 110/70. Pulse was 80, respiration 16.

The first and second days post partum were uneventful, the patient had no complaints—the blood pressure remained normal. On the third postpartum day, after being up and about, she developed what was described by the nurse as a grand mal seizure—she lost consciousness, bit her tongue, and developed clonic and tonic contractions of the muscles. Examination after seizure revealed a blood pressure of 110/70, pulse 80, respiration 20. The patient was confused but had no complaint of pain. She was given three grains of Sodium Amytal. Four hours later she developed another seizure and at this time her pulse was 144, she was unconscious and remained in a state of status epilepticus. Intravenous Sodium Amytal and Pentothal were given continuously to keep the patient quiet. In the next twenty-four hours her temperature gradually increased to 107° F. and for a while could not be determined as it went off the thermometer. A spinal tap was done and gross blood was found in the spinal fluid. A neurologist saw the patient and it was recommended that intravenous sedation be continued and the patient be wrapped in alcohol-soaked sheets with ice bag to head and armpits. The breathing became very poor, the patient was cyanotic, and artificial respiration was applied, using a mask with oxygen and carbon dioxide gas to start her breathing again.

Convulsions stopped after twenty-four hours but the patient remained comatose for the following thirteen days. She was fed by intravenous fluids and a stomach tube. Her temperature gradually returned to normal on the twelfth day. She was hallucinated for a while, but her mind gradually cleared completely and she was discharged from the hospital on the twenty-second postpartum day.

Arteriograms showed a normal internal carotid artery and normal-appearing anterior and middle cerebral vessels on the left. On the right the internal carotid artery filled but no dye entered the anterior or middle cerebral artery. It was felt that there was an occlusion of the right internal carotid artery.

The patient was entirely well one year after her recovery.

## Summary

1. A case of subarachnoid hemorrhage complicating pregnancy is reported.

2. This case may well be of the primary type and probably occurred at the sites of congenital aneuryms of the circle of Willis. There is a question of oxytocics serving as a precipitating factor, since there was a rise in blood pressure following their administration. Their indiscriminate use may lead to rupture of a congenital intracranial aneurysm even though this condition is not suspected.

3. The infrequency of subarachnoid hemorrhage complicating labor is established so far as published reports are concerned.

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1101 Beacon Street.

# RHABDOMYOSARCOMA OF THE UTERUS*

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*(From the Department of Obstetrics and Gynecology, Northwestern University Medical School)*

RHABDOMYOSARCOMAS are so designated because of their microscopic similarity to embryonic skeletal muscle. They are uncommon and are usually found in the bladder, cervix, sarcoma botryoides), and in skeletal musculature, especially in infants. They are extremely rare in the uterine fundus. Here apparently the so-called mixed mesodermal tumors are more common. There are anywhere from 12 to 94 of these latter reported in the literature, depending upon whose criteria are used for the diagnosis. These tumors contain cartilage, bone, and/or glandular elements in addition to the embryonic striated muscle-like tissue. It is probable that some of the embryonal rhabdomyosarcomas without other elements have been classified with and reported as "mixed mesodermal" tumors.

Mrs. N. P., a 57-year-old Negro, gravida ii, para i, and 10 years postmenopausal, was first seen on July 15, 1949, complaining of a foul bloody discharge. She had first noted a foul watery discharge in January, 1949, was examined at Cook County Hospital, and had refused surgery for a "tumor." In the past 3 months there had been episodes of heavy bleeding, fever to 101° F., and weight loss of 7 pounds in the last month.

She was well-nourished, with a necrotic fungating tumor filling the upper half of the vagina. The uterus was the size of a 10 weeks' pregnancy and free, although there was some induration in the right parametrium. It could not be determined whether the tumor arose from the cervix or uterus because of the excessive bleeding produced by examination.

At Wesley Memorial Hospital one week later the cervix again could not be identified. Biopsy produced heavy bleeding and a radium bomb of 175 mg. was applied for a total of 1,920 mg. hr. Five hundred c.c. whole blood (red blood count 3.49 million, hemoglobin 10.5 Gm.) was given and the patient returned to the clinic for deep x-ray therapy. On August 9 the tumor was about one-third of its previous size and was seen to protrude through a 7 cm. dilated cervical os. The uterus was of normal size.

An August 29 the x-ray therapy was stopped as the white count fell to 2,000 per cubic millimeter. The patient was readmitted to the hospital on September 13 because of an homologous serum jaundice (7 weeks after transfusion). She was discharged, still jaundiced but improved, September 21.

On October 11 she was readmitted to the hospital, the tumor again filling the vagina, pushing the uterus high in the abdomen. Tumor tissue was manually evacuated, large amounts being obtained with considerable bleeding. The point of origin was found in the vicinity of what felt like a group of submucous myomas. The tumor was adherent down the right side of the uterine cavity and at two o'clock to the endocervix. The patient was discharged after one week with the uterus involuting well. Only spotting bleeding was present. It was planned to allow time for resolution of obvious infection and then to perform a hysterectomy.

When seen one week later the tumor again was protruding from the cervix which was 3 cm. dilated and the fundus was the size of a 3 months' pregnancy. The parametria were not indurated. The following day the uterus was manually evacuated as before, the cervix sutured closed and the vagina thoroughly cleansed with iodine and alcohol. Abdominal total hysterectomy with a 4 cm. vaginal cuff and bilateral salpingo-oophorectomy were performed. There was no evidence of extension, uterine perforation, or gross lymphatic metastasis. The uterus contained intramural and submucous myomas and the wall was extremely thin in some

*Supported in part by a cancer control grant from the National Cancer Institute of the National Institutes of Health, United States Public Health Service.

Fig. 1.

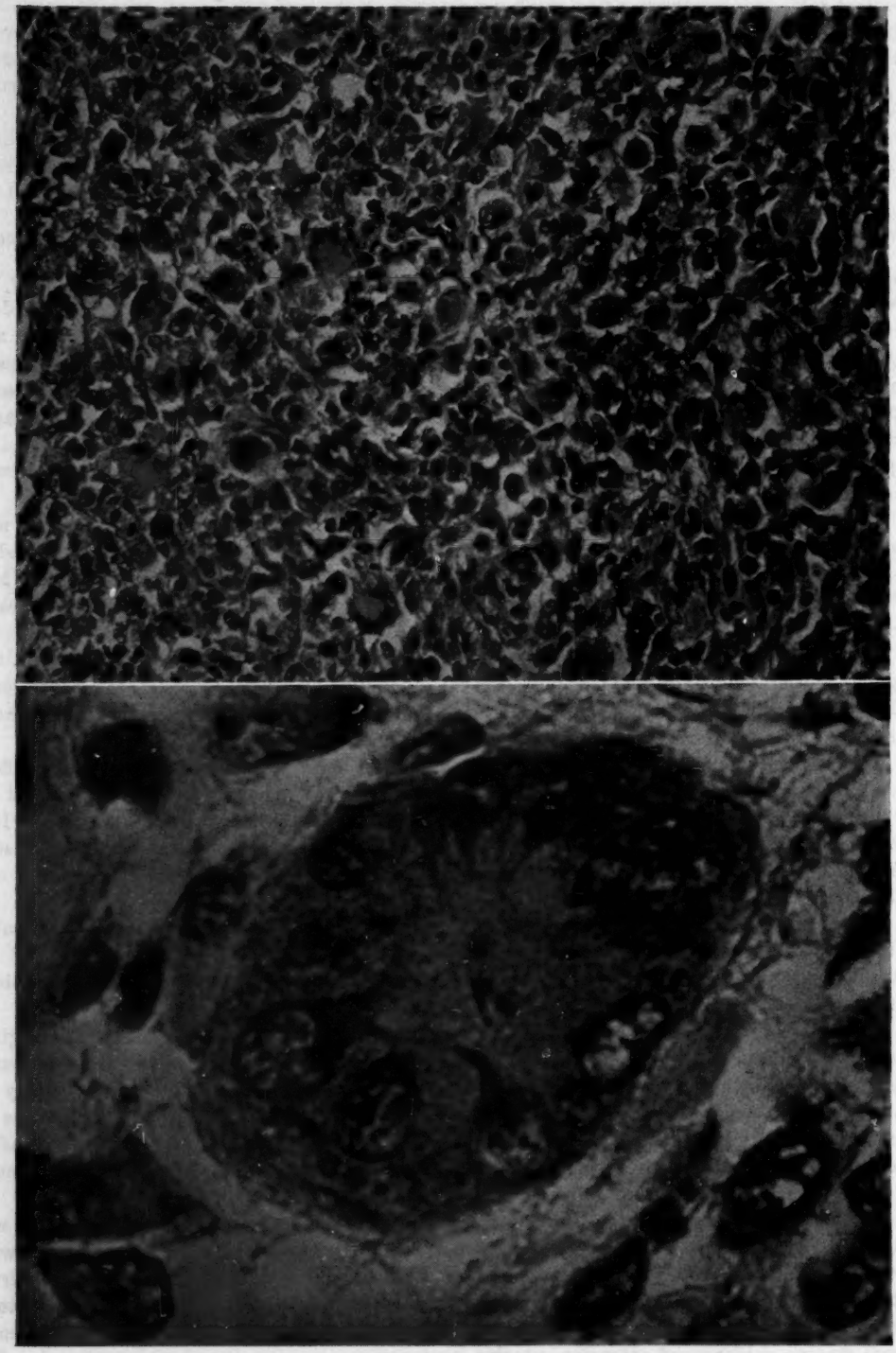

Fig. 2.

Fig. 1.—Typical area from rhabdomyosarcoma arising in the uterine fundus. (×300.)
Fig. 2.—Multinucleated cell showing so-called bearded nuclei typical of these tumors. (×2,400.)

areas. The patient was discharged 7 days later (Nov. 4, 1949) after an uneventful immediate convalescence. Deep x-ray therapy was again instituted.

On November 18, an implant 2 mm. in diameter was removed from the vaginal vault. Microscopically, it was recurrent sarcoma. A month later another recurrence was noted which grew from 1.5 by 1.0 cm. to 3 by 4 cm. in 2 days. Local radium application caused slough and decrease in discharge. Chest x-ray at this time showed lung metastasis. Previous films had been normal.

The patient was last seen Jan. 17, 1950, and was then comfortable. She died early in March 1950, after a rapidly downhill course, beginning in February. The exact cause of death was not determined as autopsy was not obtained.

The microscopic appearance of the surgical specimen was basically the same as that of the biopsies and had not been modified by the radiation. The tumor was obviously malignant with marked variation in nuclear size and shape. Mitotic figures were numerous and many were abnormal, multipolarity causing bizarre configurations (Fig. 1). There was variation in different fields but in general the individual cells had a large amount of eosinophilic cytoplasm. Large, relatively round multinucleated cells were frequent. In many of these "bearded nuclei" were prominent (Fig. 2). This appearance seems to be due to interconnecting strands or streamers of nucleoplasm between the various nuclei. In fact it seemed as though the nuclei were so affectionate that they were loath to separate completely.

Another type of multinucleated cell consisted of elongated blobs of cytoplasm with a variable number of interspersed nuclei. Intracellular longitudinal fibrils could be seen in the larger cells and definite cross striations were present in a few. These could be seen with the Milligan trichrome, periodic acid, and with phosphotungstic acid hematoxylin stains, but with none were they sufficiently sharply defined for photographic purposes.

## Summary

A case of rhabdomyosarcoma of the uterine fundus is described which grew with terrifying rapidity. Seen late, the disease progressed rapidly to a fatal termination in spite of radiation and surgical treatment.

303 East Chicago Avenue

# THE ENDOCERVICAL BIOPSY CURETTE*

## An Instrument for Detection of Early Carcinoma of the Cervix

JEROME SCHWARTZ, M.D., LYNBROOK, N. Y.

THE examination of smears of exfoliated cells for the detection of early carcinoma of the cervix has proved to be of inestimable value. Most authorities agree, however, that there are definite limitations to this method as a diagnostic procedure. Ayre,[1] Novak,[2] and others state that exfoliative cytology should never be made the basis for radical treatment, but that the diagnosis should be definitely established by adequate biopsy before therapy is instituted. Galvin and Te Linde,[3] and Younge[4] clearly demonstrate that with the increase in the number of cervices biopsied, there will be an increase in the number of preclinical cervical carcinomas detected.

Pund and Auerbach,[5] Novak,[6] and others are in agreement that the squamous margin of the squamocolumnar junction is the point of origin of the squamous cervical carcinoma. Ayre[7] and Gusberg[8] state that it is advisable to excise the entire squamocolumnar junction in order to obtain the true pathological evidence of early carcinoma. Thus, in order to detect the greatest number of early carcinomas of the cervix, biopsy should include the entire circumference of the endocervical canal, including the squamocolumnar junction. This should be a routine procedure rather than a selective operation.

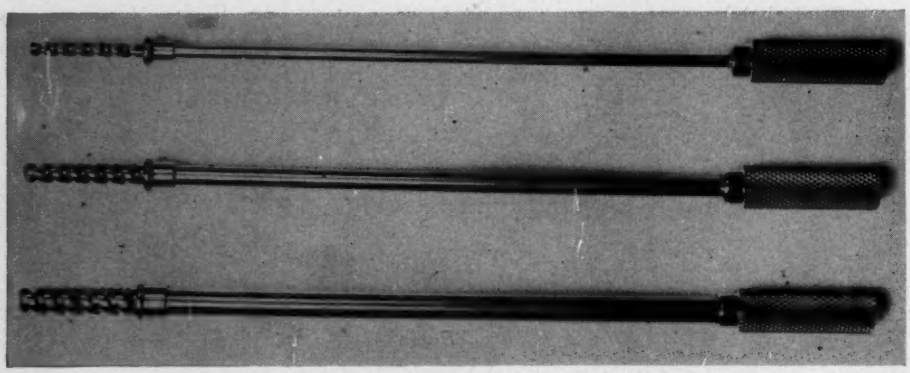

Fig. 1.

The purpose of this article is to present an endocervical biopsy curette which makes it possible to biopsy the entire endocervical canal as a simple routine office procedure attended with a minimum of discomfort to the patient, with practically no risk of cervical bleeding, and requiring no anesthesia.

Fig. 1 illustrates three such endocervical curettes of graduated size. The instrument is made of stainless steel, the cutting edge of which resembles an ordinary mechanical bit. The trailing edge of the twist is surgically sharp. In situ, the instrument acts as a multi-bladed curette. This greatly enhances the certainty of completely coning out the entire endocervical canal.

With the patient in the lithotomy position, the cervix is steadied by a tenaculum on the anterior lip. The curette is chosen which fits snugly into the cervical canal. The curette is rotated in a clockwise direction into the cervical canal up to the guard. The

*Manufactured by Kny-Sheerer Corp., 35 East 17th Street, New York, 3, N. Y.

guard prevents perforation of the uterine wall by overenthusiastic wielding of the curette. The curette is then gently pulled out, removing the epithelium of the endocervical canal. If the canal is irregular in shape, it may be necessary to reinsert the curette and angulate it slightly in order to cone out the entire endocervical lining. If a great deal of endocervical mucus is present, the mucus will fill the grooves of the curette, preventing the cutting edges from removing any tissue. Wiping the edge of the instrument with a sterile gauze will remove the mucus and the curette is then reinserted in the usual fashion. The mucus is submitted along with the biopsy specimen as a microscopic neoplastic surface lesion might be trapped within the mucus plug. Fig. 2 depicts a section of the endocervical canal obtained with this curette. The squamocolumnar junction is well illustrated.

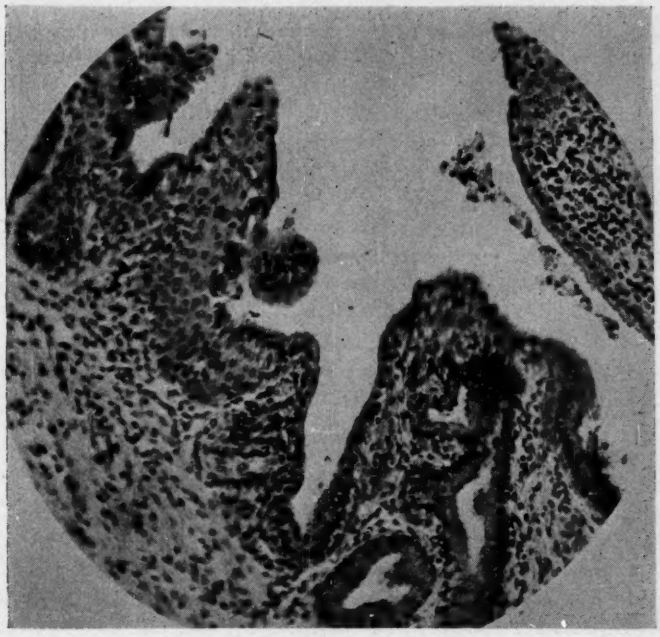

Fig. 2.

As the technique in using this instrument is simple and not time consuming, endocervical biopsy can be performed in the ordinary routine gynecological examination of the patient. As there is practically no bleeding and no discomfort attendant on this procedure, the patient is able to leave the office immediately following the biopsy.

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134 Hempstead Avenue

# BILATERAL FOLLICULAR RUPTURE

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THE following report is the second case of bilateral follicular rupture that has been seen at operation by the author. The first report was published in 1949.[1] An intensive review of the literature at that time failed to reveal any previously recorded similar case. The present patient differs in this respect: Instead of the stigmas of bilateral ovulation being present, as in the first case reported, bilateral hemorrhagic corpora lutea were found, indicating that simultaneous ovulation had taken place from each ovary some time before.

Mrs. E. D., case No. 6916, a 30-year-old married Negro woman, para i, gravida i, was admitted to the gynecological service of Harlem Hospital on April 17, 1951, with the following history: Her last normal menstrual period had been Feb., 12, 1951, lasting four days; on March 31, 1951, she bled for two days, and there had been no vaginal bleeding since that time; on the night of April 16, 1951, she suddenly developed sharp, excruciating abdominal pain, felt nauseated, and fainted "several" times; the sharp pain persisted for 24 hours and then became a "heavy feeling" which made it difficult for her to straighten up.

Menstruation began at 11 years of age and was regular in cycles of 28 days, the periods lasting four days. There was no dysmenorrhea or leukorrhea.

The patient had had a normal full-term spontaneous delivery of a 7 pound, 8 ounce child 10 years ago. There had been no subsequent pregnancies.

The past history was essentially negative. Venereal disease was denied.

*Physical Examination.*—The patient was an obese Negro woman who did not appear to be in any acute distress. The blood pressure was 120/70, pulse 80, temperature 99° F. The abdomen was obese, muscle guarding was present, and rebound tenderness was elicited throughout the entire lower abdomen. There was dullness to percussion in both flanks. Pelvic examination revealed the external genitals normal. The introitus was parous and the vaginal walls well supported. The cervix pointed anteriorly, was slightly softened and tender on motion. The fundus was in second-degree retroversion, but could not be outlined completely because of the patient's panniculus and tenderness. There was a smooth, tender, cystic mass measuring 5 by 3 cm. high in the right fornix. The left fornix was also tender to palpation with a sense of fullness but with no definite mass. Recto-vaginal examination confirmed these findings. The cul-de-sac was tender with a slight bulging sensation.

Catheterized urine was essentially negative. Red blood cell count was 4,680,000 and the hemoglobin was 12 Gm. White blood cell count was 11,200 and the erythrocyte sedimentation rate was within the normal limits of the method used in this hospital.

*Hospital Course.*—Because of the possibility of ectopic pregnancy, a cul-de-sac puncture was done using a No. 18 spinal needle, and old, dark blood was freely withdrawn. A diagnosis of right tubal abortion was made. Three hours after admission a laparotomy was performed with the following findings: The uterus was the size of a 6 weeks' pregnancy, soft and hemorrhagic in appearance; 100 c.c. of dark red blood were free in the cul-de-sac; both Fallopian tubes were grossly normal, and neither one contained visible evidence of an ectopic pregnancy; the left ovary contained a dark red hemorrhagic cyst, 4 by 3 cm., with active bleeding from a site of rupture on its posteroinferior aspect; the right ovary contained a similar cyst, 4 by 2 cm., also hemorrhagic in appearance , but un-

ruptured; each cyst at resection revealed a yellow, wavy, granular border that was part of the ovarian wall of the cyst. The operation consisted of resection of both cysts, securing of hemostasis with continuous atraumatic lock sutures, and removal of the blood from the cul-de-sac.

Aschheim-Zondek tests done postoperatively were negative. The patient was discharged from the hospital on the tenth postoperative day and has been seen in follow-up clinic twice since. She is well and is having normal regular periods.

*Pathology Report.*—The microscopic pathological findings were as follows: Section A.—This section was a portion of ovary showing the presence of a huge corpus luteum body with central hemorrhage. The corpus luteum cells presented a mild degree of vacuolization. The cytoplasm stained a pale pink, and the nuclei were centrally located. There was marked extravasation of blood around the external periphery of the corpus luteum as well as among the cords of the lutein cells. One also saw considerable extravasation of blood into the adjacent stroma. Section B.—This section was also a portion of ovary showing a corpus luteum body equal in size to that of its opposite member. The microscopic findings were identical with those of Section A and it was the opinion of the examiner that both corpus luteum bodies were apparently of similar age and development, although their actual age in reference to follicular rupture could not be definitely fixed.

*Comment.*—This is the second case of bilateral follicular rupture seen at operation by the author. Although it is well known that dissimilar twins do occur, these are the only two cases in the literature where evidence is produced to show that both ovaries have ovulated at the same time in the menstrual cycle. The first case reported, in 1949, was seen two to three days after ovulation and presented the problem of the differential diagnosis of *Mittelschmerz* from other pelvic pathology. The case reported herein is also one of bilateral follicular rupture, this one following two months of amenorrhea, and here the ruptured follicles had formed hemorrhagic corpora lutea one of which had ruptured, spilling blood into the peritoneal cavity and presenting a picture typical of tubal abortion. The microscopic examination of both specimens excluded the possibility of there being one fresh corpus luteum and one persistent corpus luteum cyst, and showed that both ovaries contained corpora lutea of approximately the same chronological age.

## Summary

A case of bilateral follicular rupture, the second seen at operation by the author, is described. No similar case reports have been found in the literature.

The author wishes to express his thanks to Dr. Solomon Weintraub for his help in interpreting the microscopic sections described, and to Dr. Peter Murray, Director of Gynecology, for his help in this presentation.

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# Department of Book Reviews

EDITED BY PHILIP F. WILLIAMS, M.D., PHILADELPHIA, PA.

## Review of New Books

### Gynecology

The third edition of this book[1] includes surgical procedures and is different from the first edition (1932) and the second one (1946) which discussed only the conservative treatment of the inflammatory diseases of the female sex organs. The book is divided into three parts. In the first one the author describes the origin, the course, and the spreading of an acquired infection, the technique of the physical examination, and the importance of the laboratory tests for the diagnosis and differential diagnosis. In the second part, the treatment of nonspecific inflammatory diseases of the vulva, the vagina, the cervix, the body of the uterus, the adnexa, and the parametrium is thoroughly discussed. The third part deals with gonorrhea and tuberculosis. The modern treatment of gonorrhea consists of the use of penicillin and sulfonamides. For the rare cases which do not respond to antibiotics, the old conservative treatment is described too exhaustively. Abdominal surgery is more frequently used with good results, because the penicillin and the sulfonamides shorten the time of the acute and subacute stages and the danger of peritonitis is greatly reduced by the preoperative and postoperative treatment with antibiotics. Tuberculosis of the sex organs is considered as a secondary disease. The general management of these cases and the x-ray treatment of tuberculosis are outlined. The effect of the irradiation is the destruction of the tuberculous granulation tissue which will be replaced by sound granulations. There is no direct influence of the x-rays on the tubercle bacilli themselves. Two instructive pictures in color of a tuberculous endometritis and a tuberculous endosalpingitis close this book, which is certainly of interest to the general practitioner and the medical student who are able to understand the German language.

ROBERT TAUBER

This is a 119-page book, bound attractively in buckram, with gold lettering. The paper is ordinary and the printing only fair. The eleven-inch height of the book makes it too high for many bookcases and unhandy for ordinary desk use for which it is designed.

The purpose of this manual,[2] it is stated, is to fill the needs of record librarians in hospitals and tumor registries, teachers of oncology, research workers, and statisticians.

Preparation of the manual was done by a committee composed of three statisticians and one pathologist, all of whom are or have been in public health work. The manual is said to be designed for use in conjunction with or as a supplement to the Standard Nomenclature of Diseases and Operations of the American Medical Association so extensively used by hospital record librarians. It is regrettable therefore that someone without immediate or remote connections with the Federal Administration did not have firsthand

[1] **Die Behandlung entzundlicher Genitalerkrankungen der Frau.** By G. Doderlein, Direktor der Universitats-Frauenklinik in Jena. Third edition. 130 pages with 19 illustrations. Leipzig, 1951, Georg Thieme Verlag. DM 9.

[2] **Manual of Tumor Nomenclature and Coding.** Prepared by Subcommittee of the Statistics Committee, American Cancer Society. 119 pages. New York, 1951, American Cancer Society. $2.50.

participation in what appears as a highly inbred effort. One of the many competent record librarians attached to our voluntary hospitals would have been a desirable addition to this committee.

The introduction explains the purpose of this manual. In addition, it contains such occasional bizarre statements that one wonders whether they are intended seriously, viz., page 9, "The histogenesis of a tumor can be evaluated correctly only through the use of a microscope." The apparent inference is that the histogenesis of any tumor is always determinable with a microscope! On this same page, the inference is also made, without qualification, that the *degree* of malignancy of a tumor is always determinable. On page 10 it is stated that "virilizing adenomas arise in the adrenal gland, benign arrhenoblastomas arise in the ovary," etc. The apparent conclusion expressed here that virilizing adenomas do not arise in the ovary and that ovarian arrhenoblastomas may not be adenomas will be completely misleading to those not versed in oncology, as will the inference that arrhenoblastomas are necessarily benign.

In order to give the codifying portion of the manual proper consideration, the reviewer sought the aid of Miss Jean Orr, an experienced registered record librarian long familiar with the use of the Standard Nomenclature. Attempts to use this manual in conjunction with the 1952 edition of the Standard Nomenclature revealed at once such profound initial inconsistencies between the two, in the behavior coding, as to render their combined or supplemental use impractical, if not impossible. In addition, spot checking the etiological coding by comparing simple, specific, pathologic lesions where confusion in terminology could be excluded also consistently revealed differences between the two nomenclatures. For example, for cancer of the uterus, the etiological code numbers are: in the Standard Nomenclature, 8091; in the Cancer Society Code, 809.7; for uterine myoma, 8690A versus 866.1; for Krukenberg tumor, 8013 versus 801.8; etc.

Unless the reviewer and his consultant are totally in error, it is clear that the American Cancer Society Manual cannot be used by hospital record librarians or anyone else as a supplement to the Standard Nomenclature of the American Medical Association, because their codes do not mesh. The Cancer Society manual also adds nothing that the Standard Nomenclature does not provide.

The limited space provided for reviews hardly permits any philosophic speculation. However, one cannot help but be puzzled and impelled to speculate about a number of problems which this current effort of the Cancer Society arouses. First, there is the obvious and avoidable duplication of effort in producing a questionably necessary manual of nomenclature whose coding is intended to, but does not, synchronize with a long-established and officially standard nomenclature. Second, why does a voluntary and largely lay-controlled public health organization such as this try to insinuate itself into so many phases of medical activity? This includes the giving of erroneous advice to the public concerning certain diagnostic procedures, efforts to take over postgraduate instruction of practicing physicians by various types of subsidization highly reminiscent of Federal bureaucratic socialization techniques, and now the production of this manual. The answer to this question probably lies in the fact that the Cancer Society has difficulty in finding legitimate or quasi-legitimate avenues for the expenditure of its funds. Those who are directing its activities must feel that these funds must be rapidly expended, not economically utilized, so that more can be asked for at each successive annual drive. Obviously, wise administration of Cancer Society moneys so as to provide funds to bona fide research workers and not to W.P.A. facsimiles thereof and to further the dissemination of proper information about cancer to the public, which is its prime function, would make annual drives for funds unnecessary. Also, the elimination of the horde of full-time jobholders at national and state levels who, like Federal bureau incumbents, have developed leechlike vested interests in their jobs, would also help conserve Cancer Society funds.

One views with misgiving and regret this poorly timed manual, which at best could have filled no great need. This could have been completely avoided had its publication been delayed but a few months until the appearance, about which they were aware, of the fourth edition of the official Standard Nomenclature of the American Medical Association.

KARL H. MARTZLOFF

This book[3] presents the lectures of the first advanced course in obstetrics and gynecology presented by the Faculty of Medicine of Montevideo. The introductory remarks were made by Rodriguez Lopez, the editor and head of the Department of Obstetrics and Gynecology of the School of Medicine of Montevideo. Likewise, the first paper in the main part of the course was given by the editor and dealt with "The Biological Hormone Diagnosis of Pregnancy and Its Scope in Medical Practice." The other papers were by Miguel Rago on "The Obstetric Problem of Cephalopelvic Disproportion"; Luis Sacco Ferraro on "Complicated Abortion: Its Distinct Clinical Picture and Its Treatment"; Rogelio Belloso on "Corrective Operations for Genital Prolapse in Women"; H. Diaz Castro (Professor of Urology) on "Pathology of Pregnancy Adaptation of the Urinary Tract and of Renal Infections During Pregnancy"; Euclides Peluffo (Professor of Pediatrics) on "Asphyxia of the Newborn"; Guillermo Piacenza on "The Problem of Cesarean Section: Seen in Its Clinical Aspects"; and Guillermo Tobler on "Dystocia Due to Soft Parts—Its Principles and Treatment." Most of the book is devoted to special lectures dealing with practical aspects of obstetric and gynecologic problems, including a special section on blood transfusions in obstetrics. The majority of these lectures were given by Rodriguez Lopez. The book clearly shows that the teachings of Rodriguez Lopez and his colleagues is conservative and in accordance with the practice of obstetrics and gynecology in the United States and elsewhere.

J. P. GREENHILL

This is a compilation of the lectures[4] presented at the third practical course in obstetrics and gynecology by the faculty of the University of Montevideo. The inaugural remarks were made by Manuel B. Rodriguez Lopez, Director of the Department of Obstetrics and Gynecology of the University of Montevideo. The book contains thirty-four papers which cover every aspect of obstetrics and gynecology. Nine of these talks were given by the editor. It is not possible to review specific articles. All of them are well presented and indicate beyond doubt that the teaching of obstetrics and gynecology in Montevideo is on a very high plane. Dr. Rodriguez Lopez is to be congratulated for having assembled this excellent book, and the others in the series of practical courses.

J. P. GREENHILL

It was inevitable that J. Ernest Ayre, well known as an assiduous worker in the field of gynecytology, should one day organize part of his extensive experience into a monograph; this he has done in **Cancer Cytology of the Uterus.**[5] The book consists of a brief text dealing with the more practical aspects of cytologic studies, together with an extensive and carefully assembled atlas of both cytologic and histologic morphology as they are related to the diagnosis of uterine cancer.

The textual material begins by discussing the basic concepts underlying the method, and here the author rightly stresses that histologic rather than cytologic study remains the basis for both diagnosis and treatment. Various standard methods of collecting ma-

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[3]**Ier Curso practico de Perfeccionamiento tocoginecologico, July, 1945.** Edited by Catedra Prof. Dr. Manuel B. Rodriguez Lopez, de la Facultad de Medicina de Montevideo. 434 pages. Montevideo, 1946, Editorial Ciencia Uruguaya.

[4]**3er Curso practico de Pedfeccionamiento tocoginecologico, July, 1947.** Edited by Catedra Prof. Dr. Manuel B. Rodriguez Lopez de la Facultad de Medicina de Montevideo. 535 pages. Montevideo, 1949, Editorial Ciencia Uruguaya.

[5]**Cancer Cytology of the Uterus.** By J. Ernest Ayre, Director, Dade County Cancer Institute, Cancer Cytology Center, and Chief, Cancer Research Department, Medical Research Foundation of Dade County, Miami, Florida. 407 pages with 362 illustrations. New York, 1951, Grune & Stratton. $14.50.

terial for cytologic study are enumerated and briefly described, special prominence being accorded Dr. Ayre's own technique of so-called "surface biopsy." Although Schiller many years ago first suggested scraping the cervix with a spoon, Ayre rightly includes a convincing discussion of the advantages of this now widely used and undeniably excellent method. Some may question the universal applicability of the author's statement that specially trained technicians can become expert in the screening out of the normal smears. Such a practice is probably sound in highly specialized centers such as those directed by Dr. Ayre, but might well lead to discrediting abuse of the method if carried out under more common and less ideal circumstances.

The classification of normal cell types which is used in the book is a slight simplification of that originally proposed by Papanicolaou and Traut, but presents no essential difference from it. The often confusing pictures of cytologic smears in patients with chronic cervicitis are admirably discussed, and there is sound comment on the relationship of chronic inflammation and cancer. In the chapter on early anaplastic cells, the author reviews his own careful morphologic analysis of the cytologic finding sometimes designated as the "precancer cell complex"—a controversial entity with which he quibbles verbally by employing the term "nearo-carcinoma" suggested by Stewart and Symeonidis. In discussing preinvasive carcinoma, Dr. Ayre emphasizes the potential importance of the surface biopsy as an agent whereby the progress of a given case can be followed; and this idea is illustrated by an impressive series of examples. A brief digression from pure cytology is made to give the recently proposed International Classification of the stages of carcinoma of the cervix which the author uses throughout the text, adopting a policy of standardization which it is to be hoped will be followed by subsequent writers on cervical cancer.

Although less precision is claimed for the diagnosis of adenocarcinoma of the endometrium than for epidermoid carcinoma of the cervix, the author is more sanguine than many cytologists of less experience concerning potential usefulness of the method in the early diagnosis of endometrial cancer. In view of the clinical features of this particular genital cancer, primary curettage remains the principal diagnostic procedure for its detection. Various methods of biopsy, including the use of a special cone-knife devised by the author, are the subject of a final chapter. Dr. Ayre stresses the necessity of obtaining a complete specimen including the entire mucocutaneous junction of the cervix, and all will surely agree with the correctness of this principle. This reviewer is inclined to doubt, however, that the use of this or any other specially designed instrument is essential for the securing of an adequate tissue specimen.

Partially interleaved with the text is an impressive array of excellent diagrams, photographs, and photomicrographs which together constitute the most attractive feature of the book. Some of these are in color, including four of Netter's decorative diagrams, but there is little to choose between the color plates and the black and white reproductions as far as clarity of detail is concerned. The publishers are due much credit for consistently superior presentation of the material. Since the author had 150,000 genital samples from over 22,000 women, including more than 900 cancer patients, from which to make his selections, the variety and exhaustiveness of his collection are most impressive. Each illustration is accompanied by a legend, sometimes terse, but more often a highly detailed commentary.

Although the ultimate significance of this work will hardly approach that of the classic monograph of Papanicolaou and Traut on the same subject, the impressive elaboration of its material and the outstanding beauty of its format are strong points in its favor. It should prove especially valuable as a manual for the use of individuals beginning the study of cytology because of its well-reproduced and thoroughly representative illustrative material and its solidly practical approach. Specialists in cytology, while they may occasionally disagree with an opinion expressed in the text, will appreciate the opportunity of owning so attractive and comprehensive an atlas of cytologic morphology.

DOUGLAS M. HAYNES

The Internatinal Jubilee Congress of the French Society[6] has published its transactions in book form, edited by Claude Béclère and Gaston Fayolle, Secretary-General and Assistant, respectively, of Scientific Contributions. It is not a complete coverage of the papers as read and submitted to the Congress. Nevertheless, it contains the presentations of gynecologists and endocrinologists of some sixteen countries, the contributors being well known in their own countries and abroad. It would take too much space for mere enumeration of the titles of the papers and the names and connections of the participants in the discussions.

The book is divided into five parts. The first part deals with gynecological endocrinology, the hypophysis, thyroid, adrenal, and ovary receiving separate consideration. Articles dealing with the estrogens, androgens, and their administration, and special articles on the endometrium are included in this section. The second part is especially devoted to sterility. The third part is concerned with gynecological syndromes; the fourth part with cancer of the cervix; the fifth part deals with gynecological surgery.

Space does not allow a résumé of the articles embraced in the book. Though tempting, it is not desirable to select for special mention those which the reviewer believes to be the more important of the many excellent papers, as each reader will naturally formulate his own opinion.

In the aggregate, the 36 papers represent a very large and important segment of gynecology and subjects which are at present under lively discussion by and of interest to all gynecologists and many other physicians. The papers all appear in French; nevertheless, the book deserves a place in the library of every specialist who possesses even the least knowledge of the French language, which in this case is facilitated by the medical terminology.

I. C. RUBIN

## Obstetrics

The title **Present Day Problems of Symphysiotomy**[7] is rather startling to a gynecologist and obstetrician who practices in North America. The operation is so very seldom performed in the United States of America.

The author, in 17 chapters, and a very extensive bibliography, gives the history of the operation, the different types of technique, and describes five. He also gives indications and contraindications to symphysiotomy and writes of its use in Latin America, especially in Uruguay. In his conclusions he advocates the technique of Zarate.

Dr. Lopez feels that the operation of symphysiotomy is indicated in small relative disproportion, is a much safer and a much easier operation than cesarean section, and that it should be performed more frequently where facilities for laparotomy are not too auspicious.

Among the complications to symphysiotomy are numbered (1) hemorrhage and hematoma; (2) anterior vaginal wall prolapse; (3) vesical and urethral trauma; (4) infection and abscess formation; (5) urinary incontinence due to lesions of the vesical neck; (6) complications of disturbances of gait due to pubic diasthesis.

The monograph ends with a list of over 250 references on the subject.

MARIO A. CASTALLO

This book[8] represents a series of articles by several contributors on common problems in obstetrics and gynecology. The scope of coverage is entirely clinical, and is pre-

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[6] **Congrès international jubilaire de la Société française de gynécologie.** By Claude Béclère, Secrétaire général pour les Travaux Scientifiques et Gaston Fayolle, Secrétaire général adjoint pour les Travaux Scientifiques. 466 pages with 89 illustrations. Paris, France, 1951, L'Expansion Scientifique Française.

[7] **Estado actual del Problema de la Sinfisiotomia.** By Manuel B. Rodriguez Lopez, Professor de Clinica Ginecotocologica de la Facultad de Medicina. 127 pages with 5 illustrations. Montevideo, Uruguay, 1951. Private publication.

[8] **Actualizaciones de Temas ginecotocologicos.** By Prof. Dr. Manuel B. Rodriguez Lopez. Faculty of Medicine, Montevideo. 451 pages with 8 figures. Montevideo, 1949, Editorial Ciencia Uruguaya.

sented in such a fashion as to be of value to the general practitioner. All in all, the material is presented as a complete didactic presentation of the clinical care of obstetric and gynecologic patients.

RUSSELL R. DE ALVAREZ

The revision of this excellent book, **The Physiology of the Newborn Infant,**[9] has been long awaited. All material has been expanded and brought up to date, and it is certain to remain the standard reference for all that pertains to the newborn infant. The book has been written by a careful student of physiology and pathology, to be readily utilized by all clinicians. Although written by a specialist in pediatrics, its topic should be of special interest to obstetricians.

The author has included all major organs and systems in his physiology of the newborn, except the central nervous system. The writing style is very comfortable, and the bibliography very complete.

The first section is devoted to respiration, and includes opinions on fetal respiratory movements and the theoretical and practical aspects of resuscitation of the newborn. The fetal hemoglobins, variable heart rates and murmurs, bleeding tendencies, cyanosis, and changing blood counts are discussed, and are followed by an excellent section on blood volume with especial relation to the time of clamping the cord. The section on the relationship of xanthochromic spinal fluid with physiological jaundice will be helpful to those trying to diagnose brain injury. The newer theories on fat absorption and neonatal tetany in premature and full-term infants are discussed.

The difficulties in interpreting renal physiology through the newer renal function tests, especially in prematures, are clearly presented, and electrolyte physiology and anaerobic metabolism in the newborn are summarized. The endocrinology section includes some of the latest work on adrenal anatomy and physiology. References are given for the management of diabetic mothers and infants born of diabetic mothers.

The outstanding chapter of the book concerns metabolism and heat regulation. The discussion of minimal, basal, and growth metabolism is carefully related to the significance of surface area and body weight. This chapter is recommended to pediatricians, to students of physiology, and to all interested in the growth and welfare of children.

The concluding section on neonatal immunology contains recommendations for immunization procedures, and serves as a reference for the heredity of blood types, allergy, and erythroblastosis.

For this superb review, there are few criticisms. The discussion of hyaline membrane was found incomplete, and no mention is made of the collapse in some prematures at the third or fourth day of life.

This book should be on the shelf of every progressive obstetrician, pediatrician, and general practitioner.

PAUL GYÖRGY

The authors of **A Pediatric Manual for Mothers**[10] have covered a wide range of subject matter that may concern any parent interested in the health and rearing of children. The question and answer format used is conducive to oversimplification, to emphasis on facts and dogma as substitutes for the basic support needed by many immature mothers. Helpful, however, are the suggestions on travel, baby sitters, toys, books, records, and comics.

ELIZABETH KIRK ROSE

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[9] **The Physiology of the Newborn Infant.** By Clement A. Smith, M.D., Associate Professor of Pediatrics, Boston Lying-in Hospital, Harvard Medical School. Second edition. 365 pages with 52 illustrations. Springfield, Ill., 1951, Charles C Thomas. $7.50.

[10] **A Pediatric Manual for Mothers.** By Harry R. Litchfield, M.D., Consultant in Pediatrics at Rockaway Beach Hospital, New York, and Leon H. Dembo, M.D., Director of Pediatrics at St. Ann's Hospital, Cleveland, Ohio. 269 pages. New York, 1951, Grune & Stratton. $2.50.

The present contribution[11] is a continuation of the worthy series of books on child development which have resulted from the more than 35 years of research in this field by Dr. Gesell and his able staff.

While this monograph is complete in itself, the text and illustrations can most fruitfully be studied in relation to one or more films made in the Institute or in the Yale Clinic of Child Development which are available for study.

The author again states his concept of growth and maturation of the child: "Maturation is the net sum of the gene effects operating in a self-limited life cycle."

The sequences in development and maturation of neuromuscular patterns, the hand, and the eye of the infant are expressed in text, in photographs, and in diagrams.

A description and interpretation of divergent patterns of development will be most useful to students of infant development.

EARL T. ENGLE

This authoritative volume, **Pathology of the Fetus and the Newborn,**[12] on the pathogenesis of all diseases affecting the fetus and newborn infant is the result of 18 years of patient and accurate observation by the leading authority in this field. The source material is drawn from the Chicago Lying-in Hospital, the Chicago Board of Health, and the many physicians who regard Edith Potter as the expert in neonatal pathology.

She combines fundamental embryologic, pathologic, and clinical data in such a way as to bring the most light possible to bear on fetal disease. Her own point of view is best expressed in her own words when she says, "The description of the body of a dead infant is of no value as an isolated piece of information, but if it is integrated with the various aspects of heredity, conception, development, intrauterine and extrauterine environment and behavior it becomes part of an important chronicle."

The material is beautifully organized and well described. The first third of the book is composed of chapters whose subject matter has broad implications such as those on rate of antenatal growth, prematurity, techniques of postmortem examination, anoxia, birth trauma, etc. The remaining two-thirds of the volume are devoted to chapters including only a single organ or organ system. Within each of these latter chapters, the individual diseases are fully and systematically described with clinical aspects stressed in correlative fashion. Several chapters include excellent and valuable tables, where indicated, and all are profusely illustrated by superb pictures.

The format is pleasing; the double columns make it very easy to read. The bibliography is extensive enough to please any student on this subject, but not so exhaustive as to overpower the reader. The indexing is of high order.

While written by a pathologist, primarily for her fellow specialists, it should in addition be in the library of every embryologist, pediatrician, and obstetrician.

ARTHUR T. HERTIG

## Miscellaneous

This little book, **Penicillin Decade,**[13] represents an excellent review of the principal published data relating to the untoward effects of penicillin therapy over the first decade of its clinical use. The authors were surprised and startled at the results of their bibliographic investigation and hence issued a word of caution regarding the indiscriminate use of penicillin. They suggested that many unnecessary reactions can be avoided if penicillin is reserved for those cases in which a bacteriologic diagnosis has been established. Theoretically, this is sound advice, but in the general practice of medicine it is

[11] **Infant Development.** By Arnold Gesell, M.D., Gesell Institute of Child Development, New Haven, Conn. 104 pages with 43 illustrations. New York, 1952, Harper & Bros. $3.50.

[12] **Pathology of the Fetus and the Newborn.** By Edith L. Potter, Associate Professor of Pathology, Department of Obstetrics and Gynecology, the University of Chicago; Pathologist, the Chicago Lying-in Hospital, Chief Pathologist, the Chicago Department of Health. 574 pages with 601 illustrations. Chicago, 1952, The Year Book Publishers, Inc. $19.00.

[13] **Penicillin Decade.** By Lawrence W. Smith, M.D., Medical Director, Commercial Solvents Corp., and Ann Dolan Walker, R.N. 122 pages. Washington, D. C, 1951, The Arundel Press, Inc. $2.50.

practically impossible, in every case, to establish an etological diagnosis before starting penicillin therapy. The clinical diagnosis alone will suffice in most instances. Mention is also made of the intradermal sensitivity test, as well as the use of the antihistaminics, or other detoxifying agents, and hypoallergic penicillins as other ways in which to reduce the great number of reactions to penicillin.

This volume is an excellent review and is recommended to medical students and to practicing physicians who desire a brief but accurate summary of the present knowledge of penicillin sensitivities.

HARRISON FITZGERALD FLIPPIN

The authors of **Antibiotic Therapy**[14] are not only well qualified but are in an enviable position to evaluate without bias the comparative merits of the various antibiotic agents. Considering the vast scope of its subject matter, this book is amazingly complete and well presented. For the first time a single volume contains information pertaining to all of the antibiotics now in general use. This book represents the best source of general information dealing with antibiotic therapy to date. The volume is recommended without reservation to students, practitioners, and teachers of medicine as an accurate, authoritative, and comprehensive book on antibiotic therapy.

HARRISON FITZGERALD FLIPPIN

**Annual Report on Stress**[15] represents the first of a series of annual supplements to the book **Stress—The Physiology and Pathology of Exposure to Stress,** by the same author, and brings the subject up to date as of 1951. Dr. Selye has for many years been engaged in evolving an elaborate system of theory concerning the general adaptation syndrome. This theory attempts to explain the manifold and complex phenomena of the alarm reaction and its projections, the stage of resistance and the stage of exhaustion, by invoking the anterior pituitary-adrenocortical axis as the principal pathway through which response to pathogenic stressors is mediated. His theory is based not only upon his own extensive researches but upon the work of numerous other investigators as well. It has been indirectly responsible to a considerable degree for the concepts which have resulted in the present recognition of the tremendous importance of the pituitary-adrenocortical axis in physiology, pathology, and clinical medicine. The present volume is divided into three parts: General Physiology and Pathology of Stress; Special Physiology and Pathology of Stress; and a Sketch for a Unified Theory of Medicine. The author attempts to explain the pathogenesis of many clinical disorders as diseases of adaptation, including such diverse entities as shock, nephrosclerosis, peptic ulcer, periarteritis nodosa, rheumatoid arthritis, etc. As he readily concedes, there are still important gaps in the theory and many cogent arguments against portions of it, but the basic importance of the entire concept of stress and its relation to human disease is so great that this supplement to the author's previous work deserves the careful attention of every student of dynamic pathology.

EDWARD ROSE

The story **One Little Boy**[16] is a well-handled manuscript bringing to light one particular psychiatric tactic in managing the complicated structure of human behavior for which no universal technique is at present known to science. Each in its own way

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[14]**Antibiotic Therapy.** By Henry Welch, Ph.D., Director, Division of Antibiotics, Food and Drug Administration, and Charles N. Lewis, M.D., Medical Officer, Division of Antibiotics Food and Drug Administration. 562 pages. Washington, D.C., 1951, The Arundel Press, Inc. $10.00.

[15]**Annual Report on Stress.** By Hans Selye, M.D., Ph.D., Professor and Director of the Institute of Medicine and Experimental Surgery, University of Montreal. 510 pages with 144 illustrations. Montreal, Canada, 1951, Acta Inc. $10.00.

[16]**One Little Boy.** By Dorothy W. Baruch. 242 pages. New York, 1952, Julian Press, Inc. $3.50.

produces results. It remains for the scientist of tomorrow to clear the cobwebs of our ignorance in human behavior, and to give us the genius so necessary in understanding the problems of mankind.

**One Little Boy** is the story of a tactical maneuver over a long period of time, by a highly specialized person, who by her special gift was capable of directing the little boy involved to a better understanding of himself; the dividends of which made him capable of living within a normal range of happiness. A cardinal fact in the treatment of the little boy was the alerting of the parents to their great shortcomings in the emotional sphere, a fact never to be ignored in the psychiatric or psychological management of children.

The author is a psychologist who has been interested in family and child relationships, and is the author of several books on the child and the parent. She brings to her work the experience of two decades in parent and child counseling.

The book is well worth reading to assay one's technique in the management of problems with children, which occur much too frequently, primarily because of inadequacy of the parents.

All physicians, regardless of their specialty, must be alerted to problems of human behavior. The obstetrician is in a particularly advantageous position, if he is aware of the problem, to give counsel and suggest early treatment when indicated.

C. NELSON DAVIS

# Department of Reviews and Abstracts

## Selected Abstracts

### Endocrinology

**Diczfalusy, E., and Westman, A.: A Study of the Effect of Intravenous Administration of Progesterone,** Acta obst. et gynec. Scandinav. 30: 315, 1951.

A preparation containing 1 per cent of crystalline progesterone in a saturated nicotinamide solution was used for administration to estrone-primed rabbits in an effort to study the effect of intravenous injection of progesterone. The effect of the preparation was estimated by studying the degree of proliferative activity in sections from the uterine cornua of sacrificed animals. In one series of experiments, the progestational potency of the nicotinamide preparation was compared with that of progesterone in oil; the nicotinamide preparation was found to be 60 to 65 per cent as potent as comparable dosages of the oil preparation. While a single dose of 20 mg. of nicotinamidized progesterone did not elicit any progestational changes in the endometrium of estrone-primed immature rabbits, it was possible to produce a progestational transformation of the endometrium in about 50 per cent of animals to whom the intravenous preparation had been administered in five 20 mg. doses within the space of 5 hours. These results indicate that progesterone administered by the intravenous route is very rapidly inactivated, so that only minute proportions of the substance actually reach the uterus. Local reactions of some severity were observed in several animals; in any event, there would not appear to be any potential use of this preparation or administration technique in gynecological practice.

DOUGLAS M. HAYNES

### Gynecology

**Brocq, P., and Robert, H.: A Review of the Baldwin-Mori Operation for Congenital Absence of the Vagina. Technics, Results, Critical Discussion of Earlier Procedures,** Gynéc. et obst. 50: 229, 1951.

The authors, from the gynecological service at l'Hôtel Dieu, Paris, report their experience with 3 cases of congenital absence of the vagina which had been overcome by employment of the Baldwin-Mori operation, with or without selected modification. In general this consists of bringing into the pelvis an ileal loop and parts of its mesoappendix, ileal transplantation, with subsequent reconversion to a circular new vaginal canal, and restoration of the small intestine by simple anastomosis.

The first case herein reported had been performed in 1913 by Lardennois of Reims and the patient was seen by Brocq and Poilleux 30 years later because of prolapse of the ileal transplant mucosa. This was repaired by surgery via laparotomy, and 37 years after the original operation the same patient was operated upon by means of a perineorrhaphy for a subsequent minor prolapse.

The authors then review 3 other cases done at their hospital and collect the world literature upon the Baldwin-Mori and other types of plastic procedures used to correct

congenital absence of the vagina. They stress the high incidence of upper pelvic and kidney anomalies in their several subseries. The lengthy article is well illustrated with 8 figures and contains a bibliography of 77 titles.

CLAIR E. FOLSOME

**Liljedahl, S. O., and Rydén, A. B.: Diagnosis and Treatment of Genital Tuberculosis in Women,** Acta Obst. et gynec. Scandinav. 30: 359, 1951.

The diagnosis and treatment of genital tuberculosis in women are discussed on the basis of the experience furnished by 148 patients in whom the diagnosis was verified histologically. Half of the patients were asymptomatic, and consulted a physician because of sterility. Analysis of the subjective symptoms of those patients presenting them indicated that the symptomatology of female genital tuberculosis does not present any pathognomonic features. Eighty per cent of the patients were afebrile, 55 per cent had no abnormal pelvic finding, and 55 per cent had normal sedimentation rates. The incidence of tuberculous peritonitis was 20 per cent, a considerably lower figure than that reported by other authors; Liljedahl and Rydén account for this low incidence by pointing out that most other reported series involve many more symptomatic patients than were studied in this instance. Tuberculous endometritis could be demonstrated in 74.2 per cent, and the over-all incidence was probably greater since the diagnosis was most often made by endometrial biopsy rather than by thorough curettage. Salpingography, using a water-soluble contrast medium, was carried out in 90 of the 148 patients, and in 87 of them the presumptive diagnosis of tuberculous salpingitis could be verified radiologically. In 3 instances, the findings were not characteristic of tubal tuberculosis. It was possible to make a correct preoperative diagnosis in 87 per cent of these cases, predominantly by the use of endometrial biopsies and salpingograms. Coexisting pulmonary tuberculous processes were present in 73 patients, but active lesions were present in only 8 of the women. Experience with this group of patients indicates that the risk of reactivation of the tuberculous process as a result of endometrial biopsy, curettage, or salpingography is negligible.

Surgical treatment, with and without supplementary radiological and antibiotic therapy, was employed in 86 patients; 44 were treated with antibiotics alone. The most commonly used surgical procedures were bilateral salpingectomy alone, or resection of Fallopian tubes with salpingostomy. Since the beginning of 1948, the authors have treated 44 women with antibiotics. Patients with confirmed tubal and endometrial tuberculosis were treated with streptomycin or PAS, and the results evaluated by means of curettage and salpingography at 3- to 4-month intervals. Streptomycin was the more effective antibiotic. In 4 cases of the 44 treated, a relapse of the endometrial tuberculosis occurred; in the other patients, the histological findings remained normal. Primary operative mortality of surgically managed patients was 4.6 per cent. Twenty of the surgically treated patients were objectively improved, and 58 of them were recorded as being asymptomatic on follow-up; 3 were not improved, and 5 succumbed. The authors suggest that patients with asymptomatic genital tuberculosis without positive physical findings on pelvic examination should not be subjected to surgery. The encouraging preliminary results obtained with antibiotics, notably streptomycin, indicate that this form of treatment should be tried before surgical intervention is considered.

DOUGLAS M. HAYNES

**Davidson, N. R.: One Hundred and Fourteen Cases of Cornual Resection in Chronic Gonorrheal Salpingitis,** West. J. Surg. 59: 319, 1951.

The advantages of cornual resection of the tubes in the treatment of chronic salpingitis and chronic pyosalpinx are described. It is re-emphasized that the gonococcus initially attacks the endocervix and the urethra and only after a period of several weeks

makes the ascent across the endometrium to the tubal epithelium. When the progress of the disease is not interrupted by antibiotics, or when reinoculation occurs, acute salpingitis is the result. In a patient whose intelligence and economic position permit a long period of medical treatment, satisfactory relief of symptoms can be obtained without surgery. If, however, she is unwilling or unable to follow the instructions and the symptoms persist with recurrent attacks of subacute salpingitis superimposed on a chronic infection, then the treatment is surgical.

Complete removal of the tubes inevitably impairs the blood supply of the ovaries. Since the infection spreads by way of the endometrium and gains access to the tubes through the cornual portion of the tubes, then why not block off the pathway over which the infection passes by simple resection of the cornua? This eliminates the need for dissection of the tube away from the ovary with the consequent trauma and makes it unnecessary to divide the recurrent ovarian branch of the uterine artery.

A series of 114 consecutive cases so treated is reported. The edematous, palpable tubes become normal in size within four weeks following cornual resection. The morbidity and the mortality rates are reduced. The patient becomes economically able to perform her duties within a short time and impairment of ovarian function is minimal.

WILLIAM BICKERS

## Newborn

**Montalvo, L., and Slocker, C.: Biology of the Infantile Vagina,** Acta ginec. 2: 183, 1951.

The authors studied the vaginas of 80 newborn infants and of 6 older girls between the ages of 6 and 11 years. They conclude that the vagina of the newborn infant has a great analogy with that of the adult female due to the maternal hormonal influences before birth.

After birth a "genital crisis" occurs, brought about by sudden deprivation of estrogens, often manifested clinically by enlargement of the breasts, edema, vaginal discharge and/or bleeding, but especially reflected in the vaginal epithelium.

After the second or third week of extrauterine life the vagina enters a stage of "functional infantile rest" which persists until the menarche.

MAGIN SAGARRA

**FitzGerald, James L., Ferris, George N., and Toshach, Clarence E.: The Influence of Maternal and Obstetrical Factors on Fetal Survival,** Am. J. M. Sc. 222: 40, 1951.

This paper presents the results of a study of the neonatal deaths and stillbirths following 3,751 deliveries. Infants were classified arbitrarily as previable if they weighed less than 1,000 grams, premature if they weighed 1,000 to 2,500 grams, and mature if they weighed over 2,500 grams.

The necessity for keeping sedation to a minimum when a premature infant is anticipated is emphasized. The preferred anesthesia to be used at delivery is low spinal, saddle or pudendal block, or local anesthesia. Inhalation anesthesia should be avoided. An incubator should be kept in readiness in the delivery room. With mature infants, much more sedation is allowed and inhalation anesthesia is permissible. The authors comment on the fact that the amount of sedation used in the delivery of a premature infant gives cause of concern to most obstetricians, whereas too little thought is given to the possible long-range effects of excessive sedation on the term infant.

In analyzing the results, it was found that 32 babies had congenital anomalies incompatible with life. In none of these cases did the mother give a history during pregnancy of viral infections, such as German measles. There were 21 cases of either stillbirth or neonatal death due to birth trauma. In reviewing these figures the authors conclude with Thoms that cesarean section should be substituted for midforceps delivery. Asphyxia was responsible for 24 combined stillbirths and neonatal deaths, atelectasis for

11, unknown factors, toxemia of pregnancy, erythroblastosis fetalis, maternal syphilis, bilateral adrenal hemorrhage, and pneumonia were each the cause of death in from 2 to 9 instances.

The obstetric factor as a predominant cause for failure of fetal survival looms in this series much larger than is generally recognized, namely, 34 per cent in premature and 46 per cent in mature infants. Breech delivery presents the greatest hazard to mature and premature infants. Better psychological preparation for labor in order to decrease the cry for sedation is urged. Premature infants have an excellent chance to survive if born without obstetric complications.

HERBERT J. SIMON

## Placenta

**Simon, J.: Placental Calcification; A Clinical Histological and Radiographic Study,** Bull. Féd. Soc. de gynéc. et d'obst. de langue franç. 3: 417, 1951.

Simon, of University Obstetric Service of the Brugmann Hospital, Brussels, evaluates his clinical, histological, and roentgenographic findings on placental calcification in a 100 case series.

By histological means, including fixation of tissue with Bouin's solution and staining with hematoxylin and eosin and masson's trichrome stain he notes that 33 placentas showed no evidence of calcium, 20 placentas gave doubtful evidence, 28 cases plus one and 19 cases plus two gradation of calcification. By roentgenographic study of 25 of those placentas exhibiting greater calcification by the histologic study the x-rays revealed a plus 4 response in 2 cases; plus 3 response in 3 cases; plus 2 response in 8 cases; plus one response in 5 case; and negative x-ray findings in 5 cases. In the more positive x-ray plates the calcium was demonstrated to be denser at the periphery of the cotelydons. There seemed to be little correlation with calcium salts and vitamin D used as prophylactic medicaments in one patient followed through two pregnancies. In brief, the deposition of calcium appeared unrelated to the antepartum use of calcium salts and vitamin D. Six figures accompany the article.

CLAIR E. FOLSOME

**Byrom, F. B.: The Antidiuretic Activity of Saline Extracts of Normal and Toxaemic Placentas,** J. Obst. & Gynaec. Brit. Emp. 58: 1, 1951.

During the past 20 years there has been considerable research done on the antidiuretic activity of extracts from the placenta. The results of such studies have not been uniform either for placentas from normal pregnancies or those from toxemic patients. The author, along with other observers, concluded that the antidiuretic effects were largely due to the presence of bacteria, contamination having taken place during the delivery or transportation and handling of the placenta. However, since the author, in the present experiments, was unable to prepare bacteria-free extracts, the possibility that the placenta may contain an antidiuretic agent cannot be excluded. The mean antidiuretic titer of extracts from the placentas of pre-eclamptic or eclamptic patients was not significantly different from those from normal patients. It therefore must be conceded that unless absolute sterility can be maintained in all placentas no definite conclusions can be drawn.

HARVEY B. MATTHEWS

## Toxemia

**Whitacre, Frank E., and Turner, Henry B.: High Fluid Intake in the Treatment of Eclampsia,** West. J. Surg. 59: 320, 1951.

From an obstetrical service where the management of severe pre-eclampsia and eclampsia is almost a daily problem comes a report dealing with the treatment of the toxemias. Presented is an account of treatment of 25 eclamptic patients. All of these

patients survived. The treatment employed was a simple one and productive of prompt clinical improvement characterized by clearing of the sensorium, early diuresis, and restoration of the patient to a clinical state where delivery could be accomplished within a period of 48 to 72 hours.

The pathologic physiology of eclampsia is primarily related to disturbed intracellular fluid balance. Although extracellular water may be present in abnormally high degree, the cells of vital organs are in a state of relative dehydration. The histologic changes in the liver and kidney are the reason and not the cause of the violent physiologic and clinical signs of the disease. The immediate problem in the convulsive patient is control of the seizures. This is accomplished by intravenous Sodium Amytal and maintained by subcutaneous phenobarbital sodium. Digitalis is occasionally employed in patients with signs of impending myocardial failure.

The sheet anchor of treatment is fluid replacement and this is accomplished by continuous intravenous 5 per cent glucose in distilled water at the rate of about one drop per second to the amount of 4,000 c.c. daily. Fluid intake and output are recorded.

Obvious peripheral tissue edema is not considered a contraindication for the administration of continuous intravenous fluid. Hematocrit determination and other laboratory evidence suggest that the toxemic patient is in a state of tissue dehydration even though excessive deposition of water might be present in the subcutaneous tissues.

Although pulmonary edema has been kept constantly in mind as a possible complication of this treatment, no case has developed thus far. On the basis of what little information is available relative to the intracellular and extracellular water and electrolyte disturbances accompanying the toxemias of pregnancy, this treatment would seem rational and the experience of these authors brings clinical confirmation.

WILLIAM BICKERS

**Kapeller-Adler, Mme.: The Metabolism of Histidine and Histamine in Normal and Toxemic Pregnancy,** Bull. Féd. Soc. de gynéc. et d'obst. de langue, franç. 3: 417, 1951.

The author, from Edinburgh, reviews the biochemical aspects and findings of histidine and histamine in normal and abnormal obstetric cases. She observes that histidinuria, while useful even as a possible pregnancy test, when urinary specimens are suitably studied, is also useful to evaluate toxemias of pregnancy. There were decreased levels of histidine in the pre-eclamptic and only traces to no histidine in the urine of eclamptic women. In 25 normal pregnancies she demonstrates high levels of serum histaminase and in 12 cases of pre-eclampsia there were generally even higher levls of plasma histaminase activity though 4 of these showed no striking increase.

Among 15 patients studied while in labor Kappeller-Adler found increased histamine and its concentration was greater in the plasma than red blood cells. The activity of the histaminase decreased toward the end of labor. In 9 cases studied during the puerperium the author found only traces of histamine in blood plasma.

In following the levels of histaminase through the antepartum period the writer observed noticeable levels of histaminase toward the end of the second month, reaching its maximal levels between the twenty-second and twenty-sixth weeks of pregnancy, gradually dropping to the twenty-eighth week at which time it remains at a stationary level until labor begins.

The author observes that the natural estrogens greatly increase the activity of histaminase, estradiol giving the greatest and estriol the least effect. Conversely, synthetic estrogens seem to inhibit the production of histaminase as do the gonadotropins. Seventeen tables accompany the article.

CLAIR E. FOLSOME

**Sauramo, H.: On the Clinical Picture and Developmental Pathology of Gestosis in the Light of Genetics,** Acta obst. et gynec. Scandinav. **30**: 338, 1951.

A large series of patients, 45,473 gravidas, is analyzed from the standpoint of the relationship between incidence of pregnancy toxemia and constitutional factors. The four principal factors analyzed are blood pressure, medical history, weight, and height. The patient who is least likely to develop pregnancy toxemia is relatively hypotensive, gives a history of continuing good health, is of normal average weight, and is relatively tall. In the series studied, 10 per cent of the women were hypotensive, 70 per cent normotensive, and 20 per cent hypertensive. The incidence of toxemia was 9.2 per cent in the hypotensive group, as compared with 45 per cent in the hypertensive group. Since the incidence of obesity is greater in the hypertensive group than in the others, the incidence of toxemia in obese individuals is correspondingly high. Chronic diseases were found to bear direct relationship to the incidence of toxemia; these included tonsillitis, scarlet fever, glomerulonephritis with nephrosclerosis, and rheumatic fever. When the material was divided into categories according to weight, the frequency of toxemia was found to be 45 per cent in the overweight group, 27.5 per cent in the underweight group, and 19 per cent in the normal weight group. In different height groups, there was a significantly higher incidence of toxemia in the short patients as compared with the tall patients; the combination of short stature and obesity resulted in a 56 per cent incidence of toxemia.

DOUGLAS M. HAYNES

**Pigeaud, H.: Eclampsia Developing in Early Stages of a Hydatidiform Mole,** Gynéc. et obst. **48**: 470, 1949.

The author, from Lyon, describes in detail a case of typical eclampsia developed in the fourth month of pregnancy. Actually the patient, a 25-year-old, para i, gravida ii, exhibited a hydatidiform mole, an ovarian luteal cyst, and a great increase in serum gonadotropins. The uterus was of about the size of a 4-month pregnancy. She rapidly developed a marked generalized edema, a blood pressure range of 160/90 to 175/100, and only traces of proteinuria. She was admitted to the hospital in convulsions. She aborted the hydatidiform mole after a 4-day bougie induction approximately one month after hospital admittance and was discharged from the hospital 13 days following expulsion of the hydatidiform mole and its accompanying hemorrhage. Examination 4 months later found the patient in excellent health. The serum gonadotropin level 18 days before expulsion of the mole was 60,000 units; 1,000 units 13 days after expulsion and 120 units per liter.

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